OXYMORPHONE HYDROCHLORIDE- oxymorphone hydrochloride tablet
Aurolife Pharma, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use oxymorphone hydrochloride tablets safely and effectively. See full prescribing information for oxymorphone hydrochloride tablets.

OXYMORPHONE HYDROCHLORIDE TABLETS, for oral use CII
Initial U.S. Approval: 1959

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF OXYMORPHONE HYDROCHLORIDE TABLETS

See full prescribing information for complete boxed warning.

- **Oxymorphone hydrochloride tablets expose users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)**
- **Life-threatening respiratory depression can occur at any time during the course. Monitor closely, especially upon initiation or following a dose increase. (5.2)**
- **Accidental ingestion of oxymorphone hydrochloride tablets, especially by children, can result in a fatal overdose of oxymorphone. (5.2)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these products in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.3, 7)**
- **To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, evaluate patient risk for opioid addiction, abuse, or misuse. Evaluation and Mitigation Strategy (REMS) for these products. (5.5)**
- **Prolonged use of oxymorphone hydrochloride tablets may increase the risk of the Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by gastroenterology experts will be available if this occurs. (5.6)**
- **Instruct patients not to consume alcohol or any product containing alcohol while taking oxymorphone hydrochloride tablets because co-ingestion can result in fatal plasma oxymorphone levels. (5.8)**

RECENT MAJOR CHANGES

Indications and Usage (1)	10/2025
Dosage and Administration (2.2, 2.6)	10/2025
Warnings and Precautions (5.1, 5.2, 5.3, 5.12, 5.14)	10/2025

INDICATIONS AND USAGE

Oxymorphone hydrochloride tablets is indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1.1)

Limitations of Use
Because of the risks of addiction, abuse, and misuse, overdose and death which can occur at any dosage or duration and persist over the course of therapy, reserve opioid analgesics, including oxymorphone hydrochloride tablets, for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1.1)

DOSAGE AND ADMINISTRATION

- Oxymorphone Hydrochloride Tablets should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks. (2.1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. Reserve higher dosages for patients in whom lower doses, regimens, or other opioids have been insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks. (2.1)
- Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available. (2.1)
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse. (2.1, 5.1)
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dose increases with oxymorphone hydrochloride tablets. Consider this risk when selecting an initial dose and when making dose adjustments. (2.1, 5.2)
- Initiate treatment with oxymorphone hydrochloride tablets in a dosing range of 10 mg to 20 mg every 4 to 6 hours as needed for pain at the lowest dose necessary to achieve adequate pain relief. Titrate the dose based on the individual patient's response to their initial dose of oxymorphone hydrochloride tablet. (2.3)
- Oxymorphone hydrochloride tablets should be taken on an empty stomach, at least one hour prior to or two hours after eating. (2.1)
- Discuss opioid overdose reversal options and options for acquiring them with the patient and/or caregiver, both when initiating and renewing treatment with oxymorphone hydrochloride tablets, especially if there are additional risk factors for overdose, or close contacts at risk for exposure and overdose. (2.2, 4, 5.1, 5.2, 5.5)
- Conversion to oxymorphone hydrochloride tablets: Follow recommendations for conversion from other opioids to oxymorphone hydrochloride tablets.
- Hepatic Impairment: Initiate treatment with 5 mg and titrate slowly. Monitor for signs of respiratory and central nervous system depression. (2.9)
- Renal Impairment: Initiate treatment with 5 mg and titrate slowly. Monitor for signs of respiratory and central nervous system depression. (2.9)
- Elderly, Cachectic, or Debilitated Patients: Initiate treatment with 5 mg and titrate slowly and/or enter for signs of respiratory and central nervous system depression. (2.9)
- Patients Concomitantly Ingesting Alcohol: Initiate with 10 to 20 the recommended starting dose, consider using a lower dosage strength, concomitant CNS depressant, and monitor closely. (2.3, 2.7, 5.10)
- Periodically reassess patients receiving oxymorphone hydrochloride tablets to evaluate the continued need for opioid analgesia, the development of addiction, abuse, or misuse or signs/symptoms of adverse reactions, and for the development of addiction, abuse, or misuse. (2.6) (5)
- Do not rapidly reduce or abruptly discontinue oxymorphone hydrochloride tablets in a physically dependent patient. Slowly taper oxymorphone hydrochloride tablets when a patient taking opioid analgesics has resolved in serious withdrawal symptoms, uncontrolled pain, and sudden. (2.8, 5.18)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg and 10 mg. (3)

CONTRAINDICATIONS

- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitation equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to oxymorphone, any other ingredients in Oxymorphone Hydrochloride Tablets. (4)
- Moderate or severe hepatic impairment. (4)

WARNINGS AND PRECAUTIONS

- Opioid Induced Hyperalgesia (OIH) and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an patient's pain increases from taking opioids. This may be due to OIH or tolerance. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation. (5.4)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or Elderly, Cachectic, or Debilitated Patients: Regularly evaluate potentially life-threatening respiratory depression in these patients, especially during initiation or following a dose increase. Consider monitoring with pulse oximetry or capnography in these patients. (5.7)
- Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions: Discontinue Oxymorphone Hydrochloride Tablets and other medications if any oxymorphone formulation. (5.8)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean off the opioid. (5.9)
- Severe Hypotension: Regularly evaluate during drug initiation and titration. Avoid use of Oxymorphone Hydrochloride Tablets in patients with manifest circulatory shock. (5.11)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Regularly evaluate for sedation and respiratory depression. Avoid use of oxymorphone hydrochloride tablets in patients with impaired consciousness or coma. (5.12) (5)

ADVERSE REACTIONS

Adverse reactions (≥ 2% of patients): Nausea, pruritus, nonvomiting, vomiting, pruritus, headache, constipation, dizziness, and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aurolife Pharma USA, Inc. at 1-888-958-0016 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Benzodiazepines: Concomitant use is contraindicated in serotonin syndrome.
  Monoamine Oxyrnaline Oxymorphone Hydrochloride Tablets if serotonin syndrome is suspected. (7)
- Monoamine Oxidase Inhibitors (MAOI): Concomitant use is contraindicated in patients taking Oxymorphone Hydrochloride Tablets because drug may induce analgesic effect of oxymorphone hydrochloride tablets, or precipitate withdrawal symptoms. (7)
- Cytochrome P450 3A4 Inhibitors: Concomitant use may potentiate the effects of oxymorphone. Avoid concomitant use of protease inhibitors within or within 14 days of stopping such treatment with an MAOI. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. **Revised: 12/2025**

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF OXYMORPHONE HYDROCHLORIDE TABLETS

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF OXYMORPHONE HYDROCHLORIDE TABLETS

Addiction, Abuse, and Misuse
Oxymorphone hydrochloride tablets expose patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing and reassess all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

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

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

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepine or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of oxymorphone hydrochloride tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Neonatal Opioid Withdrawal Syndrome (NOWS)
Prolonged maternal use of oxymorphone hydrochloride during pregnancy can result in Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery *[see Warnings and Precautions (5.4)]*.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription *[see Warnings and Precautions (5.5)]*.

Interaction with Alcohol
Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking oxymorphone hydrochloride tablets. The co-ingestion of alcohol with oxymorphone hydrochloride tablets may result in increased plasma levels and a potentially fatal overdose of oxymorphone *[see Warnings and Precautions (5.10)]*.

1 INDICATIONS & USAGE

Oxymorphone hydrochloride tablets is indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use
Because of the risks of addiction, abuse, and misuse, overdose and death which can occur at any dosage or duration and persist over the course of therapy *[see Warnings and Precautions (5.1)]*, reserve opioid analgesics, including oxymorphone hydrochloride tablets for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

2 DOSAGE & ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Oxymorphone hydrochloride tablets should be administered on an empty stomach, at least one hour prior to or two hours after eating *[see Clinical Pharmacology (12.3)]*.
Oxymorphone hydrochloride tablets are available as tablets for oral administration. Oxymorphone is available as both immediate-release 5 mg and 10 mg tablets and extended-release 5 mg and 10 mg tablets *[see Dosage Forms and Strengths (3)]*.
Oxymorphone Hydrochloride Tablets should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks.
Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.
Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of Oxymorphone hydrochloride tablets for patients in whom lower doses, regimens, or other opioids have been insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.
Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available.

There is variability in the opioid analgesic dose and duration needed to adequately manage pain in any patient. Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.
Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dose increases with oxymorphone hydrochloride tablets. Consider this risk when selecting an initial dose and when making dose adjustments *[see Warnings and Precautions (5)]*.

2.2 Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, or other risk factors for overdose), or if the patient's caregiver or close contacts are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.
Inform the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program) *[see Life-threatening Respiratory Depression (5.2)]*.
There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and recommended dosing. Prescribers should refer to the product-specific approved labeling for those products, prior to recommending or prescribing such an agent.

2.3 Initial Dosage

Use of Oxymorphone Hydrochloride Tablets as the First Opioid Analgesic
Initiate treatment with oxymorphone hydrochloride tablet in a dosing range of 10 to 20 mg every 4 to 6 hours as needed for pain at the lowest dose necessary to achieve adequate pain relief. Titrate the dose based on the individual patient's response to their initial dose of oxymorphone hydrochloride tablet.

Do not initiate treatment with doses higher than 20 mg because of the potential serious adverse reactions [see Clinical Studies (14.1)].

Conversion from Other Opioids to Oxymorphone Hydrochloride Tablets
There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, the dose of oxymorphone hydrochloride tablets cannot be calculated on a basis of oxymorphone hydrochloride tablets. It is safer to underestimate a patient's 24-hour oxymorphone hydrochloride tablets dosage than to overestimate the 24-hour oxymorphone hydrochloride tablets dosage and manage an adverse reaction due to overdose.

For conversion from other opioids to oxymorphone hydrochloride tablets, physicians and other healthcare professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate. In general, it is safest to start oxymorphone hydrochloride tablets therapy by administering half of the calculated total daily dose of oxymorphone hydrochloride tablets in 4 to 6 equally divided doses (e.g., 10 mg every 4 hours for a total daily dose of 20 mg), and the dose can be gradually adjusted until adequate pain relief and acceptable side effects have been achieved.

Conversion from Parenteral Oxymorphone to Oxymorphone Hydrochloride Tablets
Given oxymorphone hydrochloride tablet's absolute and bioavailability of approximately 10%, patients receiving parenteral oxymorphone may be converted to oxymorphone hydrochloride tablets by administering 10 times the patient's total daily parenteral oxymorphone dose as oxymorphone hydrochloride tablets, in four or six equally divided doses (e.g., IV dose x 10) divided by 4 or 6). For example, approximately 10 mg of

oxymorphone hydrochloride tablets four times daily may be required to provide pain relief equivalent to a total daily IM dose of 4 mg oxymorphone. Due to patient variability with regard to opioid analgesic response, upon conversion patients should be closely monitored to ensure adequate analgesia and to minimize side effects.

Conversion from Oxymorphone Hydrochloride Tablets to Extended-Release Oxymorphone.
The relative bioavailability of oxymorphone hydrochloride tablets compared to extended-release oxymorphone is unknown, so conversion to extended-release oxymorphone may lead to increased risk of excessive sedation and respiratory depression.

2.6 Dosage Modifications in Patients with Mild Hepatic Impairment

Oxymorphone hydrochloride tablets is contraindicated in patients with moderate or severe hepatic impairment.

Use oxymorphone hydrochloride tablets with caution in patients with mild hepatic impairment. Consider the lowest dose (e.g., 5 mg) and titrating slowly while carefully monitoring for signs of respiratory and central nervous system depression *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.2)]*.

2.5 Dosage Modifications in Patients with Renal Impairment

Use Oxymorphone Hydrochloride Tablets with caution in patients with creatinine clearance rates less than 50 mL/min, starting with the lowest dose (e.g., 5 mg) and titrating slowly while carefully monitoring for signs of respiratory and central nervous system depression *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

2.6 Dosage Modifications in Geriatric Patients

Exercise caution in the selection of the starting dose of oxymorphone hydrochloride tablets for an elderly patient by starting with the lowest dose (e.g., 5 mg) and titrate slowly while carefully monitoring for signs of respiratory and central nervous system depression *[see Use in Specific Populations (8.5)]*.

2.7 Dosage Modifications with Concomitant Use of Central Nervous System Depressants

Oxymorphone hydrochloride tablets, like all opioid analgesics, should be started at one-third to one-half of the usual dose in patients who are concurrently receiving other central nervous system (CNS) depressants, including sedatives, hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol. Because respiratory depression, hypotension and profound sedation, coma or death may result *[see Warnings and Precautions (5.3) and Drug Interactions (7)]*. When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced.

2.8 Titration and Maintenance of Therapy

Individually titrate oxymorphone hydrochloride tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving oxymorphone hydrochloride tablets to assess the maintenance of pain control, signs and symptoms of opioid adverse reactions, and sleep disturbances caused by opioid-induced for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1,5.16)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the oxymorphone hydrochloride tablets dosage. If after dosage increase, adverse reactions are bothersome or intolerable, but pain is controlled (including an increase in pain after dosage increase) consider reducing the dosage *[see Warnings and Precautions (5)]*. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.9 Safe Reduction or Discontinuation of Oxymorphone Hydrochloride Tablets

Do not rapidly reduce or abruptly discontinue oxymorphone hydrochloride tablets in patients who have been taking it regularly. Abrupt discontinuation or rapid dose discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid dose reduction or abrupt discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be contaminated with drug seeking behavior. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

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

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

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, evaluate patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for an
extended period of time
and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.16), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

The 5 mg dosage form is light blue to blue colored, mottled, round, uncoated tablets, debossed with 'LRS' on one side and plain on the other side.
The 10 mg dosage form is light peach to peach colored, mottled, round, uncoated tablets, debossed with 'LRM' on one side and plain on the other side.

4 CONTRAINDICATIONS

Oxymorphone hydrochloride 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 (5.6)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.12)]*
- Hypersensitivity to oxymorphone (e.g., anaphylaxis, angioedema) or *[see Warnings and Precautions (5.7), Adverse Reactions (6)]*
- Moderate or severe hepatic impairment *[see Warnings and Precautions (5.15)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse
Oxymorphone hydrochloride tablets contains oxymorphone, a Schedule II controlled substance. As an opioid, oxymorphone hydrochloride tablets expose users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed oxymorphone hydrochloride tablets. Addiction can occur at recommended dosages and if the drug is misused or abused. The risk of opioid-related addiction is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in most patients with these disorders. The abuse liability of oxymorphone hydrochloride tablets, but use in such patients necessitates intensive counseling about the risks and proper use of oxymorphone hydrochloride tablets along with frequent reevaluation of the risk of developing addiction and misuse. Consider recommending or prescribing opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing oxymorphone hydrochloride tablets. Assess each patient's risk for opioid addiction, abuse, or misuse in the smallest appropriate quantity and advising the patient on careful storage of the drug during the course of treatment and the proper disposal of unused drug. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.
5.2 Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and circulatory arrest. Management of respiratory depression may include close observation, supportive measures, and use of opioid overdose reversal agents, 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 oxymorphone hydrochloride tablets, the risk is greatest during the initiation of therapy or following a dosage increase.

To reduce the risk of respiratory depression, proper dosing and titration of oxymorphone hydrochloride tablets are essential *[see Dosage and Administration (2)]*. Oversedation and hypoventilation like that from other opioid analgesics may occur in patients from another opioid product *can result in a fatal overdose with the first dose.*

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

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

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

Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose.
Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion
or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient *[see Warnings and Precautions (5.1, 5.3)]*.

Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program).

There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for these products, prior to recommending or prescribing such an agent.

Educate patients and caregivers on how to recognize respiratory depression, and how to administer an opioid overdose reversal agent in the emergency treatment of overdose. Emphasize the importance of calling 911 or getting emergency medical help, even if an opioid overdose reversal agent is administered *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.3), Overdosage (10)]*.

5.3 Risks from Concomitant Use with Benzodiazepines and Other CNS Depressants
Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on oxymorphone hydrochloride tablets therapy. The co-ingestion of alcohol with oxymorphone hydrochloride tablets may result in increased plasma levels and a potentially fatal overdose of oxymorphone *[see Clinical Pharmacology (12.3)]*.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of oxymorphone hydrochloride tablets with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin] other opioid. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

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

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid. In patients already receiving a benzodiazepine or 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 while closely monitoring for signs and symptoms of sedation and respiratory depression. If concomitant use is warranted, consider recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.2), Overdosage (10)]*.

Advise both patients and caregivers about the risks of respiratory depression and sedation when oxymorphone hydrochloride tablets 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 disorder, including misuse and addiction, and educate on the dangers and signs of overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7), Patient Counseling Information (17)]*.
5.4 Neonatal Opioid Withdrawal Syndrome
Use of oxymorphone hydrochloride tablets for an extended period of time during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatal specialists. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.
5.5 Opioid Analgesic REMS Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant educational programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:
• Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) that is designed to enhance competence on the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
• Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/Drugs/ucm084448.htm#PCG
• Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
• Assist patients by other tools to improve patient, household, and community safety, such as patient- prescriber agreements that reinforce patient-prescriber responsibilities.
To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CMECS, call 1-855-533-5766, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/Drugs/ucm084448.htm#Blueprint.
5.6 Opioid-Induced Hyperalgesia (OIH)
Opioid-induced hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, in that the dose of opioid needed to maintain a given level of pain relief may have to be increased (see Dependence (9.3)). Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease to explain the observed pain, or other signs of disease progression.
Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, it may be appropriate to gradually reduce the dose of the current opioid analgesic, or opioid rotation (safely switching the patient to a different opioid molecule) *[see Dosage and Administration (2.3), Warnings and Precautions (5.16)]*.
5.7 Use in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients
The use of oxymorphone hydrochloride tablets in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: Oxymorphone Hydrochloride Tablets -treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of oxymorphone hydrochloride tablets *[see Warnings and Precautions (5.3)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (8.5)]*.

Regularly evaluate patients, particularly when initiating and titrating oxymorphone hydrochloride tablets and when oxymorphone hydrochloride tablets is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions*

(5.2,5.22). Drug interactions (7)). Alternatively, consider the use of non-opioid analgesics in these patients.

5.8 Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions
Potentially life-threatening hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients treated with oxymorphone hydrochloride tablets. In the majority of cases, the onset of these reactions occurred within the first hour; reports were swelling of the face, eyes, mouth, lips, tongue, hands, and/or throat; dyspnea; hives; pruritus; and/or rash; and nausea/vomiting. If anaphylaxis or other hypersensitivity occurs, stop administration of oxymorphone hydrochloride tablets immediately, discontinue oxymorphone hydrochloride tablets permanently, and do not rechallenge with oxymorphone hydrochloride tablets. Instruct patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction (*see Patient Counseling information (17)*).

5.9 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 tests as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dose 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.

5.10 Severe Hypotension
Oxymorphone hydrochloride tablets may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) (*see Warnings and Precautions (5.2) and Drug Interactions (7)*). Monitor these patients for signs of hypotension after initiating or titrating the dosage of oxymorphone hydrochloride tablets. In patients with circulatory shock, oxymorphone hydrochloride tablets may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of oxymorphone hydrochloride tablets in patients with circulatory shock.

5.11 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), Oxymorphone hydrochloride tablets may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor these patients for signs of sedation and respiratory depression, particularly when initiating therapy with oxymorphone hydrochloride tablets.

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

5.12 Risks of Gastrointestinal Complications
Oxymorphone hydrochloride tablets is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

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

Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids for long periods of time and in patients who have had a history of opioids increase. Regularly evaluate patients for signs and symptoms of OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain), and if necessary, adjust opioid therapy as clinically appropriate. (*see Clinical Pharmacology (12.2)*).

5.13 Increased Risk of Seizures in Patients with Seizure Disorders
The oxymorphone in oxymorphone hydrochloride tablets may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures occurring in other clinical settings associated with seizures. Regularly evaluate patients with a history of seizure disorders for worsened seizure control during oxymorphone hydrochloride tablets therapy.

5.14 Withdrawal
Do not rapidly reduce or abruptly discontinue oxymorphone hydrochloride tablets in a patient physically dependent on opioids. When discontinuing oxymorphone hydrochloride tablets in a patient physically dependent, gradually taper the dosage. Rapid tapering of oxymorphone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain (*see Dosage and Administration (2.9), Drug Abuse and Dependence (9.3)*)

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including oxymorphone hydrochloride tablets. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms (*see Drug Interactions (7)*).

5.15 Risks of Driving and Operating Machinery
Oxymorphone hydrochloride tablets may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of oxymorphone hydrochloride tablets and know how they will react to the medication.

5.16 Hepatic Impairment
A study of extended-release oxymorphone tablets in patients with hepatic disease indicated greater plasma concentrations than in those with normal hepatic function (*see Clinical Pharmacology (12.3)*). Use oxymorphone hydrochloride tablets with caution in patients with mild impairment, starting with the lowest dose and titrating slowly while carefully monitoring for side effects (*see Dosage and Administration (2.3, 2.4)*). Oxymorphone hydrochloride tablets is contraindicated in patients with moderate or severe hepatic impairment.

5.1 Addiction, Abuse, and Misuse

5.1 Addiction, Abuse, and Misuse
Oxymorphone Hydrochloride Tablets contains oxymorphone, a Schedule II controlled substance. As an opioid, Oxymorphone Hydrochloride Tablets exposes users to the risks of addiction, abuse, and misuse (*see Drug Abuse and Dependence (9)*).

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Oxymorphone Hydrochloride Tablets. Addiction can occur at recommended dosages and the risk is increased in patients with an addiction disorder. Overdose or overdose-related death is increased with higher opioid doses, and the risk persists over the course of therapy. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use (*see Adverse Reactions (6.2)*).

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing Oxymorphone Hydrochloride Tablets, and reassess all patients receiving Oxymorphone Hydrochloride Tablets for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The presence of one or more these risk factors should not prevent the management of pain in any given patient. Patients at increased risk may be prescribed opioids such as Oxymorphone Hydrochloride Tablets, but use in such patients necessitates intensive counseling about the risks and proper storage and disposal of Oxymorphone Hydrochloride Tablets along with frequent reevaluation for signs of addiction, abuse, and misuse. Consider prescribing or recommending opioid overdose reversal agent (*see Dosage and Administration (2.2), Warnings and Precautions (5.2)*).

Opioids are sought for nonmedical use and are subject to diversion from legitimate channels. Prescribers and other healthcare providers should guard against abuse of Oxymorphone Hydrochloride Tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on careful storage of the drug during the course of treatment and the proper disposal of unused drug. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even those taken as directed in presumptive patients. If not recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid overdose reversal agents, 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 Oxymorphone Hydrochloride Tablets, the risk is greatest during the initiation of therapy or following a dosage increase.

To reduce the risk of respiratory depression, proper dosing and titration of Oxymorphone Hydrochloride Tablets are essential (*see Dosage and Administration (2)*). Overestimating the Oxymorphone Hydrochloride Tablets dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of Oxymorphone Hydrochloride Tablets, especially by children, can result in respiratory depression and death due to an overdose of oxymorphone.

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

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

Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose.

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdoses or if there are household members (including children) or other close contacts at risk for accidental ingestion
or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient (*see Warnings and Precautions (5.1, 5.3)*).

Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program).

There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for each agent, when prescribing an opioid overdose reversal agent.
Educate patients and caregivers on how to recognize respiratory depression, and how to use an opioid overdose reversal agent for the emergency treatment of opioid overdose. Emphasize the importance of calling 911 or getting emergency medical help, even if an opioid overdose reversal agent is administered (*see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.3), Overdosage (10)*).

5.3 Risks from Concomitant Use with Benzodiazepines and Other CNS Depressants

Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on Oxymorphone Hydrochloride Tablets therapy. The co-ingestion of alcohol with Oxymorphone Hydrochloride Tablets may result in increased plasma levels and a potentially fatal overdose of oxymorphone (*see Clinical Pharmacology (12.3)*).

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Oxymorphone Hydrochloride Tablets with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin] and other opioid. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

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

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of the other drug. In patients already receiving an opioid analgesic, if a benzodiazepine is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Inform patients and caregivers of this potential interaction, educate them on the signs and symptoms of respiratory depression (including sedation). If concomitant use is warranted, consider recommending or prescribing an opioid overdose reversal agent (*see Dosage and Administration (2.2), Warnings and Precautions (5.2), Overdosage (10)*).

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

5.4 Neonatal Opioid Withdrawal Syndrome
Use of Oxymorphone Hydrochloride Tablets for an extended period of time during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike withdrawal in adult patients, is life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (*see Use in Specific Populations (8.1), Patient Counseling Information (17)*).

5.5 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. As a condition of FDA approval, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:
• Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
• Discuss the risks of opioid use, risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/Drugs/DrugSafety/REMS/PCG.
• Emphasize to patients and their caregivers the importance of reading the Medication Guide they receive from their pharmacist every time an opioid analgesic is dispensed to them.
• Consider using other tools to improve patient, household, and community safety, such as naloxone and other medications to treat opioid overdose, when appropriate.
To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-855-543-3784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/Drugs/DrugSafety/REMS/ucm111351.htm.

5.6 Opioid-Induced Hyperalgesia and Allodynia

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

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid or opioid rotation (see Dosage and Conversion Factors for Opioid Analgesics Risks) (see Dosage and Administration (2.3); Warnings and Precautions (5.16)).

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

The use of Oxymorphone Hydrochloride Tablets in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: Oxymorphone Hydrochloride Tablets -treated patients with chronic pulmonary diseases are susceptible to life-threatening respiratory depression at doses 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 Oxymorphone Hydrochloride Tablets (see Warnings and Precautions (5.20).

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 (8.5)).

Regularly evaluate patients, particularly when initiating and titrating Oxymorphone Hydrochloride Tablets and when Oxymorphone Hydrochloride Tablets are used concomitantly with other drugs that depress respiration [see Warnings and Precautions (5.3,5.2), Drug Interactions (7)]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.8 Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions

Potentially life-threatening hypersensitivity reactions, including anaphylaxis and angioedema, have been reported in patients taking Oxymorphone Hydrochloride Tablets in the postmarket setting. The most commonly described clinical features in these reports were swelling of the face, eyes, mouth, lips, tongue, hands, and/or throat; dyspnea; hives, pruritus, and/or rash; and nausea/vomiting. If anaphylaxis or other hypersensitivity occurs, stop administration of Oxymorphone Hydrochloride Tablets and immediately provide appropriate medical intervention. Oxymorphone Hydrochloride Tablets are not rechallenge with any formulation of oxymorphone. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction [see Patient Counseling Information (17)].

5.9 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 tests 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 extent to which adrenal insufficiency may particular opioids as being more likely to be associated with adrenal insufficiency.

5.10 Severe Hypotension

Oxymorphone Hydrochloride Tablets may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS-depressant drugs (e.g., phenothiazines or general anesthetics) [see Warnings and Precautions (5.3) and Drug Interactions (7)]. Regularly evaluate these patients for signs of hypotension after initiating or dose escalating Oxymorphone Hydrochloride Tablets to avoid hypotension with circulatory shock. Oxymorphone Hydrochloride Tablets may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Oxymorphone Hydrochloride Tablets in patients with circulatory shock.

5.11 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), Oxymorphone Hydrochloride Tablets 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 Oxymorphone Hydrochloride Tablets.

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

5.12 Risks of Gastrointestinal Complications

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

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

Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids, and may occur more frequently in patients taking higher doses of opioids and/or in patients taking opioids longer term [see Warnings and Precautions (5.12)]. Regularly evaluate patients for signs and symptoms of OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain), and if necessary, adjust opioid therapy as clinically appropriate. [see Clinical Pharmacology (12.2)].

5.13 Increased Risk of Seizures in Patients with Seizure Disorders

The oxymorphone in oxymorphone hydrochloride tablets may increase the frequency of seizures in patients with seizure disorders, and may aggravate convulsions in some patients occurring in other clinical settings associated with seizures. Regularly evaluate patients with a history of seizure disorders for worsened seizure control during oxymorphone hydrochloride tablets therapy.

5.14 Withdrawal

Do not rapidly reduce or abruptly discontinue oxymorphone hydrochloride tablets in a patient physically dependent on opioids. When discontinuing oxymorphone hydrochloride tablets in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxymorphone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain [see Dosage and Administration (2.9), Drug Abuse and Dependence (9.3)].

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a pure opioid analgesic, such as oxymorphone hydrochloride tablets. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms [see Drug Interactions (7)].

5.15 Risks of Driving and Operating Machinery

Oxymorphone hydrochloride tablets may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Oxymorphone Hydrochloride Tablets and know how they will react to the medication.

5.16 Hepatic Impairment

A study of extended-release oxymorphone tablets in patients with hepatic disease indicated greater plasma concentrations than in those with normal hepatic function [see Clinical Pharmacology (12.3)]. Use Oxymorphone hydrochloride tablets with caution in patients with mild impairment, starting with the lowest dose and titrating slowly while monitoring for adverse effects [see Dosage and Administration (2.5, 2.6)]. Oxymorphone hydrochloride tablets is contraindicated in patients with moderate or severe hepatic impairment.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.6)]*
- Interactions with Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.3)]*
- Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions *[see Warnings and Precautions (5.8)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.9)]*
- Severe Hypotension *[see Warnings and Precautions (5.10)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.12)]*
- Seizures *[see Warnings and Precautions (5.13)]*
- Withdrawal *[see Warnings and Precautions (5.14)]*
- Opioid-Induced Hyperalgesia and Allodynia [See Warnings and Precautions (5.6)]

6.1 Clinical Trials Experience

Adult 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 practice.

A total of 591 patients were treated with oxymorphone hydrochloride tablets in controlled clinical trials. The clinical trials consisted of patients with acute post-operative pain (N=557) and cancer pain (n=34) trials.

The following table lists adverse reactions that were reported in at least 2% of patients receiving oxymorphone hydrochloride tablets in placebo-controlled trials (acute post-operative pain (N=557)).

Table 1: Adverse Reactions Reported in Placebo-Controlled Trials

MedDRA Preferred Term	Oxymorphone Hydrochloride Tablets (N=557)	Placebo (N=279)
Nausea	20%	12%
Pyrexia	14%	8%
Somnolence	9%	2%
Vomiting	8%	7%
Pruritus	8%	4%
Headache	7%	4%
Dizziness (Excluding Vertigo)	7%	2%
Constipation	4%	1%
Confusion	3%	<1%

The **common** (≥1% to <10%) adverse drug reactions reported at least once by patients treated with oxymorphone hydrochloride tablets in the clinical trials organized by MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class were and not represented in Table 1.

Cardiac disorders: tachycardia

Gastrointestinal disorders: dry mouth, abdominal distention, and flatulence
General disorders and administration site conditions: sweating increased
Nervous system disorders: sedation, anxiety and vertigo
Respiratory, thoracic and mediastinal disorders: hypoxia
Vascular disorders: hypotension

Other less common adverse reactions known with opioid treatment that were seen <1% in the oxymorphone hydrochloride tablets trials includes the following:

Abdominal pain, ileus, diarrhea, agitation, disorientation, restlessness, feeling jittery, hypersensitivity, allergic reactions, bradycardia, central nervous system depression, depressed level of consciousness, lethargy, mental impairment, mental status changes, tremor, muscle twitching, muscle rigidity, muscle weakness, paresthesia, dysgeusia, dysphagia, dysphoria, edema, euphoric mood, hallucination, hypertension, insomnia, miosis, nervousness, palpitation, postural hypotension, syncope, dyspnea, respiratory depression, respiratory distress, respiratory rate decreased, oxygen saturation decreased, difficult micturition, urinary retention, urticaria, skin blurred, visual disturbances, weakness, appetite decreased, and weight decreased.

6.2 Post-marketing Experience

The following adverse reactions have been identified during post approval use of opioids. Since 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.

Nervous system disorder: amnesia, convulsion, memory impairment

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
Anaphylaxis: Anaphylaxis has been reported with ingredients contained in oxymorphone hydrochloride tablets.

Immune System Disorders: Angioedema, and other hypersensitivity reactions.

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

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

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

Opioid-induced esophageal dysfunction (OIED): Cases of OIED have been reported in patients taking opioids, and may occur more frequently in patients taking higher doses of opioids and/or in patients taking opioids longer term [see Warnings and Precautions (5.12)].

Adverse Reactions from Observational Studies

A prospective, observational cohort study estimated the risks of addiction, abuse, and misuse in patients initiating long-term use of Schedule II opioid analgesics between 2017 and 2021. Study participants included in one or more analyses had been enrolled in selected insurance plans or health systems for at least one year, were free of at least one opioid use disorder and opioid overdose, and had no cancer diagnosis and either: 1) filled multiple-extended-releasing-acting opioid analgesic prescriptions during a 90 day period (n=870); or 2) filled any Schedule II opioid analgesic prescriptions covering at least 70 of 90 days (n=1,246). Those included also had no dispensing of the qualifying opioids in the previous 6 months.
Study results:
• approximately 2% to 6% of participants across the two cohorts newly met criteria for addiction, as assessed with two validated interview-based measures of moderate-to-severe opioid use disorder based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria, and
• approximately 1% to 3% of participants across the two cohorts newly met criteria for prescription opioid abuse and misuse (defined in Drug Abuse and Dependence (9.2)) respectively, as measured with a validated self-reported instrument.

A retrospective, observational cohort study estimated the risk of opioid-involved overdose and opioid-related death in patients initiating long-term use of opioid Schedule II opioid analgesics from 2006 through 2016 (n=220,246). Included patients had been enrolled in either one of two commercial insurance programs, one managed care program, or one Medicaid program for at least 9 months. New long-term use was defined as having Schedule II opioid analgesic prescriptions covering at least 70 days' supply in the first 90 days of initiation, and no opioid use in the previous 6 months. Patients were excluded if they had an opioid-involved overdose in the 6 months prior to study entry. Overdose was measured using a validated medical code-based algorithm with linkage to the National Death Index database. The 5-year cumulative incidence estimates for opioid-involved overdose or opioid overdose-related death ranged from 0.22% to 0.42% for the three study cohorts, depending on the study site and length of follow-up. Approximately 2.7% of first opioid overdoses observed over the entire study period (5-11 years, depending on the study site) were fatal. Higher baseline opioid dose was the strongest risk factor for overdose, including opioid-involved overdose or opioid overdose-related death. Study exclusion criteria may have selected patients at lower risk of overdose, and substantial loss to follow-up (approximately 40%) also may have biased estimates.
The risk estimates from the studies described above may not be generalizable to all patients receiving opioid analgesics, such as those with exposures shorter or longer than the duration evaluated in the studies.

7 DRUG INTERACTIONS

Table 2 includes clinically significant drug interactions with oxymorphone hydrochloride tablets.

Alcohol	
Clinical Impact:	The concomitant use of alcohol with Oxymorphone Hydrochloride Tablets can result in an increase of oxymorphone plasma levels and potentially fatal overdose of oxymorphone.
Intervention:	Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on oxymorphone hydrochloride tablets therapy [see Clinical Pharmacology (12.3)].
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Inform patients and caregivers of this potential interaction, educate them on the signs and symptoms of respiratory depression (including sedation). If concomitant use is warranted, consider monitoring patients for signs of sedation and respiratory depression. Avoid agent [see Dosage and Administration (2.2, 2.7), Warnings and Precautions (5.1, 5.3, 5.5)]
Examples:	benzodiazepines and other sedatives/hypnotics, anxiolytics tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids (gabapentin or pregabalin), other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue oxymorphone hydrochloride tablets if serotonin syndrome is suspected.
Examples:	selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see Warnings and Precautions (5.8)]. The risk of severe adverse reactions is increased when administration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.
Intervention:	The use of oxymorphone hydrochloride tablets are not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of oxymorphone hydrochloride tablets and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.

Examples	Butorphanol, nalbuphine, pentazocine, buprenorphine.
Muscle Relaxants	
Clinical Impact	Oxymorphone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention	Because respiratory depression may be greater than otherwise expected decrease the dosage of oxymorphone hydrochloride tablets and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider administering an opioid antagonist prior to neuromuscular blocking agent *(see Dosage and Administration (2.2), Warnings and Precautions (5.2-5.6))*.
Examples	cyclobenzaprine, metaxalone
Diuretics	
Clinical Impact	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention	Evaluate patients for signs of urinary retention or reduced gastric motility when oxymorphone hydrochloride Tablets are used concomitantly with anticholinergic drugs.
Anticholinergic Drugs	
Clinical Impact	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention	Evaluate patients for signs of urinary retention or reduced gastric motility when oxymorphone hydrochloride tablets are used concomitantly with anticholinergic drugs.
Tranquilizers	
Clinical Impact	Tranquilizer can potentiate opioid-induced respiratory depression.
Intervention	Evaluate patients for respiratory depression when oxymorphone hydrochloride tablets and tranquilizer are used concurrently.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome *(see Warnings and Precautions (5.4) and Clinical Considerations)*. Data from randomized controlled trials with oxymorphone use in pregnant women during labor and delivery have been conducted. However, these studies were not designed to identify a drug-associated risk for major birth defects and miscarriage because oxymorphone exposure occurred after the first trimester. There are reports of respiratory depression in infants in some of these trials *(see Clinical Considerations)*.

In animal reproduction studies, reduced postnatal survival of pups and an increased incidence of stillborn pups were observed following oral treatment of pregnant rats with oxymorphone during gestation at doses approximately 2 times and 4 times the human daily dose of 30 mg/day (HDD), respectively. Reduced fetal weights were observed with oral administration of oxymorphone to pregnant rats and rabbits during organogenesis at exposures up to 6.9 and 68.8 times the HDD, 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

Use of opioid analgesics for an extended period of time during pregnancy for medical or nonmedical purposes may result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *(see Warnings and Precautions (5.4))*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid overdose reversal agent, such as naloxone or nalmefene, should be available for use in the treatment of respiratory depression in the neonate. Oxymorphone Hydrochloride tablets is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Oxymorphone Hydrochloride tablets is not recommended for use in women 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 oxymorphone hydrochloride from Gestation Day 6 to 17 via oral gavage doses of 5, 10, or 25 mg/kg/day (2.4, 4.9, or 12.2 times the HDD based on body surface area, respectively). Reduced mean fetal weights were observed at 4.9 times the HDD. Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights in all groups and mortality in the high dose group).

Pregnant rabbits were treated with oxymorphone hydrochloride from Gestation Day 7 to 20 via oral gavage doses of 10, 35, or 58 mg/kg/day (9.8, 34.4, or 68.8 times the HDD based on body surface area, respectively). Decreased mean fetal weights were noted at 68.8 times the HDD. Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights).

Pregnant rats were treated with oxymorphone hydrochloride from Gestation Day 6 to Lactation Day 20 via oral gavage doses of 5, 10, or 25 mg/kg/day (6.5, 2.4, 4.9, or 12.2 times the HDD based on body surface area, respectively). Increased neonatal death (postnatal day 0-1) was noted at 2.4 times the HDD. Decreased pup survival over postnatal day 0-4 was noted at 12.2 times the HDD. Decreased maternal weights were noted at 4.9 times the HDD. Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights in all groups and mortality in the 10 and 25 mg/kg/day groups).

In a published study, neural tube defects (exencephaly and craniorachis) were noted following subcutaneous administration of 15.9 mg/kg oxymorphone hydrochloride (62.2 times the HDD) on Gestation Day 8 to pregnant hamsters. This dose also produced significant maternal toxicity (20% maternal deaths).

8.2 Lactation

Risk Summary

There is no information regarding the presence of oxymorphone in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for oxymorphone hydrochloride tablets and any potential adverse effects on the breastfed child from oxymorphone hydrochloride tablets or from the underlying maternal condition.

Clinical Considerations

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

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for oxymorphone hydrochloride tablets and any potential adverse effects on the breastfed infant from oxymorphone hydrochloride tablets or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility

Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *(see Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1))*.

8.4 Pediatric Use

Safety and effectiveness for pediatric patients, 0 to 17 years, have not been established.

An open-label study was conducted in 58 pediatric patients 12 years of age and older with postoperative pain using oxymorphone hydrochloride tablets. Efficacy was not demonstrated in this population treated with doses expected to be comparable to those used in adults. Results of a study in adolescent patients suggest that treatment with oxymorphone hydrochloride tablets resulted in substantially higher systemic exposures to oxymorphone in 2 out of 24 patients.

Oxymorphone Hydrochloride Tablets are not recommended for use in the pediatric population.

8.5 Geriatric Use

Oxymorphone hydrochloride tablets should be used with caution in elderly patients *(see Clinical Pharmacology (12.3))*.

Of the total number of subjects in clinical studies of oxymorphone hydrochloride tablets, 30% were 65 and over, while 7% were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects. There were several adverse events that were more frequently observed in subjects 65 and over compared to younger subjects. These adverse events included dizziness, somnolence, constipation, and nausea. Elderly patients should be administered the drug with caution, 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 administered concomitantly with other drugs that depress respiration. Titrate the dosage of oxymorphone hydrochloride tablets slowly in geriatric patients and frequently reevaluate the patient for signs of central nervous system and respiratory depression *(see Warnings and Precautions (5.6))*.

Oxymorphone 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 the elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to regularly evaluate renal function.

8.6 Hepatic Impairment

In a study of extended-release oxymorphone tablets, patients with mild hepatic impairment were shown to have an increase in bioavailability compared to the subjects with normal hepatic function. Oxymorphone Hydrochloride Tablets should be used with caution in patients with mild impairment. These patients should be started with the lowest dose (5 mg) and titrated slowly while carefully monitoring for signs of respiratory and central nervous system depression. Oxymorphone Hydrochloride Tablets are contraindicated for patients with moderate and severe hepatic impairment *(see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.15), and Clinical Pharmacology (12.3))*.

8.7 Renal Impairment

In a study of extended-release oxymorphone tablets, patients with moderate to severe renal impairment were shown to have an increase in bioavailability compared to the subjects with normal renal function *(see Clinical Pharmacology (12.2))*. Such patients should be started with the lowest dose (5 mg) and titrated slowly while monitoring for signs of respiratory and central nervous system depression *(see Dosage and Administration (2.5) Clinical Pharmacology (12.2))*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Oxymorphone Hydrochloride Tablets contains oxymorphone, a Schedule II controlled substance.

9.2 Abuse

Oxymorphone hydrochloride tablets contains oxymorphone, a substance with high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction *(see Warnings and Precautions (5.1))*.

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

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

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

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

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because chronic use of opioids may lead to misuse, abuse, or addiction even under appropriate medical care. Patients at high risk of oxymorphone hydrochloride tablets abuse include those with a history of prolonged use of any opioid, including products containing oxymorphone, those with a history of drug or alcohol abuse, or those who use oxymorphone hydrochloride tablets in combination with other abused drugs.

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

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

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

Risks Specific to Abuse of Oxymorphone Hydrochloride Tablets

Abuse of oxymorphone hydrochloride tablets poses a risk of overdose and death. The risk is increased with concurrent use of oxymorphone hydrochloride tablets with alcohol and/or other CNS depressants.
Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

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

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

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

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may occur to a clinically significant degree until after several days to weeks of continued use.

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

When discontinuing oxymorphone hydrochloride tablets, gradually taper the dosage using a patient-specific plan that considers the following: the dose of oxymorphone hydrochloride tablets immediately prior to the dose reduction, the clinical signs of the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient.

In patients taking opioids for an extended period of time at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *(see Dosage and Administration (2.1), and Warnings and Precautions (5.11))*.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *(see Use in Specific Populations (8.1))*.

10 OVERDOSAGE

Clinical Presentation

Acute overdose with oxymorphone hydrochloride tablets can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, cardiac arrest, and death. Miosis may persist after anoxia has ensued. It has been seen with hypoxia in overdose situations *(see Clinical Pharmacology (12.2))*. Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days, or weeks after apparent recovery from the initial intoxication.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support measures.

For clinically significant respiratory or circulatory depression secondary to oxymorphone overdose, administer an opioid overdose reversal agent such as naloxone or nalmefene.

Because the duration of opioid reversal is expected to be less than the duration of action of oxymorphone in oxymorphone hydrochloride tablets, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid overdose reversal agent is inadequate or brief, or if the patient relapses, administer additional reversal agent as directed by the products prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the opioid overdose reversal agent will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome will depend on the duration and degree of physical dependence and the dose of the reversal agent administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the reversal agent should be initiated with care and by titration with smaller than usual doses of the reversal agent.

11 DESCRIPTION

Oxymorphone Hydrochloride Tablets (oxymorphone hydrochloride) is an opioid agonist available in 5 mg and 10 mg tablet strengths for oral administration. The chemical name for oxymorphone hydrochloride is 4, 5a-epoxy-2, 14-dihydroxy-17-methylmorphinan-6-one hydrochloride. The molecular weight is 337.80. The molecular formula is $C_{17}H_{19}NO_4$ · HCl and it has the following chemical structure:

Oxymorphone hydrochloride is white to off white odorless powder, which is sparingly soluble in alcohol and ether, but freely soluble in water.
The inactive ingredients in Oxymorphone Hydrochloride Tablets include lactose monohydrate, magnesium stearate, microcrystalline cellulose and pregelatinized starch. In addition, the 5 mg tablets contain FD&C Blue No. 2 aluminum lake. The 10 mg tablets contain FD&C Red No. 40 aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxymorphone 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 oxymorphone is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with oxymorphone.

Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Oxymorphone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Oxymorphone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked myoclonic rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Oxymorphone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone in the entire colon may be increased, 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 and opioid-induced esophageal dysfunction (OIED).

Effects on the Cardiovascular System

Oxymorphone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans (*see Adverse Reactions 6.2*). They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Use of opioids for an extended period of time may influence the hypothalamic-pituitary-adrenal axis or pituitary-gonadal axis in ways that may result in clinical signs of hypogonadism, 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 in animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationship

The minimum effective analgesic concentration varies widely among patients, especially those who are tolerant to the analgesic effects of other opioids administered chronically or opioids. The minimum effective analgesic concentration of oxymorphone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance (*see Dosage and Administration (2.1, 2.2)*).

Concentration-Adverse Reaction Relationship

There is a relationship between increasing oxymorphone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions (*see Dosage and Administration (2.1, 2.3, 2.7)*).

12.3 Pharmacokinetics

Absorption

The absolute oral bioavailability of oxymorphone is approximately 10%. Studies in healthy volunteers reveal predictable relationships between oxymorphone hydrochloride tablet dosage and plasma oxymorphone concentrations.

Steady-state levels were achieved after three days of multiple-dose administration. Under both single-dose and steady-state conditions, dose proportionality has been established for 5 mg, 10 mg and 20 mg doses of oxymorphone hydrochloride tablets, for both peak plasma levels (C_{max}) and extent of absorption (AUC) (see Table 2).

Table 2: Mean (±SD) Oxymorphone Hydrochloride Tablets Pharmacokinetic Parameters

Regimen	Dosage	C_{max} (ng/mL)	AUC (ng•hr/mL)	$T1/2$ (hr)
Single dose	5 mg	1.18±0.55	4.98±2.07	7.25±0.80
	10 mg	1.93±0.75	9.10±3.60	7.78±3.58
	20 mg	3.74±1.46	19.1±7.60	8.04±2.60
Multiple Doses*	5 mg	1.73±0.60	4.64±1.69	NA
	10 mg	3.51±0.91	10.19±3.24	NA
	20 mg	7.31±2.92	21.10±7.59	NA

NA = not applicable
*Results after 3 days of every 6 hours dosing.

After oral dosing with 40 mg of Oxymorphone Hydrochloride Tablets in healthy volunteers under fasting conditions or with a high-fat meal, the C_{max} and AUC were increased by approximately 38% in fed subjects relative to fasted subjects.

As a result, Oxymorphone Hydrochloride Tablets should be dosed at least one hour prior to or two hours after eating (*see Dosage and Administration (2.1)*).

Distribution

Studies on the distribution of oxymorphone in various tissues have not been conducted. Oxymorphone is not extensively bound to human plasma proteins; binding is in the range of 10% to 12%.

Metabolism

Oxymorphone is highly metabolized, principally in the liver, and undergoes reduction or conjugation with glucuronic acid in the liver and in other tissues. The two major metabolites of oxymorphone are oxymorphone-3-glucuronide and 6-OH-oxymorphone. The mean plasma AUC for oxymorphone-3- glucuronide is approximately 90-fold higher than the parent compound. The pharmacologic activity of the glucuronide metabolite has not been evaluated. 6-OH-oxymorphone has been shown in animal studies to be a potent opioid agonist. The 6-OH-oxymorphone metabolite contributes a AUC approximately 76% of the oxymorphone AUC following single-oral doses but is essentially equivalent to the parent compound at steady-state.

Excretion

Because oxymorphone is extensively metabolized, <1% of the administered dose is excreted unchanged in the urine. On average, 10% to 38% of the administered dose is excreted in the urine as oxymorphone-3-glucuronide and 0.25% to 0.62% is excreted as 6-OH-oxymorphone in subjects with normal hepatic and renal function. In animals given radiolabeled oxymorphone, approximately 90% of the administered radioactivity was recovered within 5 days of dosing. The majority of oxymorphone-derived radioactivity was found in the urine and feces.

Specific Populations

Age: Geriatric Population

The pharmacokinetics of oxymorphone administered as an extended-release tablet were about 40% higher in elderly (≥65 years of age) than in younger subjects (*see Use in Specific Populations (8.5)*).

Sex

The effect of sex on the pharmacokinetics of oxymorphone hydrochloride tablets has not been studied. In a study with an extended-release formulation of oxymorphone, there was a consistent tendency for female subjects to have slightly higher AUC_{inf} and C_{max} values than male subjects. However, sex differences were not observed when AUC_{inf} and C_{max} were adjusted by body weight.

Hepatic Impairment

The liver plays an important role in the pre-systemic clearance of orally administered oxymorphone. Accordingly, the bioavailability of orally administered oxymorphone may be increased in patients with impaired hepatic function. The effect of mild hepatic impairment on the pharmacokinetics of Oxymorphone Hydrochloride Tablets has not been studied. However, in a study with an extended-release formulation of oxymorphone, the disposition of oxymorphone was compared in 6 patients with mild, 5 patients with moderate, and one patient with severe hepatic impairment, and 12 subjects with normal hepatic function. The bioavailability of oxymorphone was increased by 1.9-fold in patients with mild hepatic impairment and by 2.7-fold in patients with moderate hepatic impairment. In one patient with severe hepatic impairment, the bioavailability was increased by 12.2-fold. The half-life of oxymorphone was not significantly affected by hepatic impairment.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of Oxymorphone Hydrochloride Tablets has not been studied. However, in a study with an extended-release formulation of oxymorphone, an increase of 26%, 57%, and 60% in oxymorphone bioavailability was observed in patients with mild (n=6), moderate (n=6), moderate (creatinine clearance 20-50 mL/min; n=6), and severe (creatinine clearance <20 mL/min; n=6) patients, respectively, compared to healthy controls.

Drug Interaction Studies

Oxymorphone is not expected to be biotransformation of oxymorphone to 6-OH-oxymorphone by any of the major cytochrome P450 (CYP P450) isoforms at therapeutically relevant oxymorphone plasma concentrations.

No inhibition of any of the major CYP P450 isoforms was observed when oxymorphone was incubated with human liver microsomes at concentrations of ≤50 µ M. An inhibition of CYP 2D6 activity was observed at concentrations greater than 50 µ M. It is not expected that oxymorphone, or its metabolites will act as inhibitors of any of the major CYP P450 enzymes *in vivo*.

Increases in the activity of the CYP 2C9 and CYP 3A4 isoforms occurred when oxymorphone was incubated with human hepatocytes. However, clinical drug interaction studies with Oxymorphone Hydrochloride Tablets 5A showed no induction of CYP450 3A4 or 2C9 enzyme activity, indicating that no dose adjustment for CYP 3A4-or 2C9-mediated drug-drug interactions is required.

Alcohol Interaction

The effect of co-ingestion of alcohol with Oxymorphone Hydrochloride Tablets have not been evaluated. However, an *in vivo* study was performed to evaluate the effect of alcohol (40%, 20%, 4% and 0%) on the bioavailability of a single dose of 40 mg of oxymorphone extended-release tablets. The results showed that the effect of concomitant administration of 240 mL of 40% ethanol the C_{max} increased on average by 70% and up to 270% in individual subjects. Following the concomitant administration of 240 mL of 20% ethanol the C_{max} increased on average by 60% and up to 220% in individual subjects. In some individuals there was also a decrease in oxymorphone peak plasma concentrations. No effect on the release of oxymorphone from the extended-release tablet was noted in an *in vitro* alcohol interaction study. The mechanism of the *in vivo* interaction is unknown. Therefore, avoid co-administration of oxymorphone and ethanol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis & Mutagenesis & Impairment Of Fertility

Carcinogenesis

No evidence of carcinogenic potential was observed in long-term animal studies in mice and rats. Oxymorphone hydrochloride was administered to Sprague-Dawley rats (2.5, 5, and 10 mg/kg/day in males and 5, 10, and 25 mg/kg/day in females) for 2 years by oral gavage. Systemic drug exposure (AUC) at the highest doses tested in male and female rats was 4.8 times and 21.2 times the human exposure at a dose of 20 mg/day, respectively. Oxymorphone hydrochloride was administered to CD-1 mice (male and female CD-1 mice (10, 25, 75 and 150 mg/kg/day) for 2 years by oral gavage. Systemic drug exposure (AUC) at 150 mg/kg/day in male and female mice was 205 times and 243 times the human exposure at a dose of 20 mg/day, respectively.

Mutagenesis

Oxymorphone hydrochloride was not mutagenic when tested in the in vitro bacterial reverse mutation assay (Ames test), or in an in vitro mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes. Oxymorphone hydrochloride tested positive in both the rat and mouse in vivo micronucleus assays. An initial mouse micronucleus assay performed with oral gavage doses of oxymorphone of ≥250 mg/kg and in rats given doses of 30 and 40 mg/kg. A subsequent study demonstrated that oxymorphone hydrochloride was not aneugenic in mice following administration of up to 500 mg/kg.

Additional studies indicate that the increased incidence of micronucleated polychromatic erythrocytes in rats may be secondary to increased body temperature following oxymorphone administration. Doses associated with increased micronucleated polychromatic erythrocytes also produced a transient increase in rat body temperature. Pretreatment of animals with sodium salicylate minimized the increase in body temperature and prevented the increase in micronucleated polychromatic erythrocytes after administration of 40 mg/kg oxymorphone.

Impairment of Fertility

Female rats were treated with oxymorphone hydrochloride beginning 14 days prior to mating through Gestation Day 7 via oral gavage doses of 5, 10, or 25 mg/kg/day (2.4, 4.8, and 12 times the human exposure at a dose of 20 mg/day, respectively). Male rats were treated via oral gavage with the same oxymorphone hydrochloride doses beginning 28 days prior to and throughout mating. In female rats, an increase in the length of the estrus cycle and decrease in the mean number of viable embryos, implantation sites and corpora lutea were observed at 4.9 times the human dose of 20 mg/day. No adverse effects of oxymorphone on male reproductive function or sperm parameters were observed.

14 CLINICAL STUDIES

The analgesic efficacy of oxymorphone hydrochloride tablets has been evaluated in acute pain following orthopedic and abdominal surgeries.

14.1 Orthopedic Surgery

Two double-blind, placebo-controlled, dose-ranging studies in patients with acute moderate to severe pain following orthopedic surgery demonstrated that oxymorphone hydrochloride tablets 10 mg and 20 mg, and 30 mg was included in one study. Both studies demonstrated that oxymorphone hydrochloride tablets 20 mg provided greater analgesia as measured by total pain relief based on a weighted analysis over 8 hours using a 0 to 4 categorical, compared to placebo. Oxymorphone hydrochloride tablets 10 mg and 30 mg were not distinguishable from placebo in one of the two studies. There was no evidence of superiority of the 30 mg dose over the 20 mg dose. However, there was a high rate of naloxone use in patients receiving the oxymorphone hydrochloride tablets 30 mg dose in the post-operative period (*see Dosage and Administration (2.3)*).

14.2 Abdominal Surgery

In a randomized, double-blind, placebo-controlled, multiple-dose study, the efficacy of oxymorphone hydrochloride tablets 10 mg and 20 mg was assessed in patients with moderate to severe pain following abdominal surgery. Patients were treated with doses dosed every 6 to 6 hours over a 48-hour treatment period. Oxymorphone hydrochloride tablets 10 and 20 mg provided greater analgesia, as measured by the mean average pain intensity on a 0 to 100 mm visual analog scale, over 48 hours, compared to placebo (*see Dosage and Administration (2.3)*).

16 HOW SUPPLIED/STORAGE AND HANDLING

Oxymorphone Hydrochloride Tablets are supplied as follows:

Oxymorphone Hydrochloride Tablets, 5 mg are light blue to blue colored, mottled, round, uncoated tablets, debossed with 5/80 on one side and plain on the other side.

Bottles of 30	NDC 13107-103-30
Bottles of 100	NDC 13107-103-01
Bottles of 1000	NDC 13107-103-49

Oxymorphone Hydrochloride Tablets, 10 mg are light peach to peach colored, mottled, round, uncoated tablets, debossed with 5/80 on one side and plain on the other side.

Bottles of 30	NDC 13107-104-30
Bottles of 100	NDC 13107-104-01
Bottles of 1000	NDC 13107-104-49

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

Dispense in tight container as defined in the USP, with a child-resistant closure (as required).

Store Oxymorphone Hydrochloride Tablets securely and dispose of properly [see Patient Counseling Information (17)].

17 PATIENT COUNSELING INFORMATION

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

Storage and Disposal
Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store Oxymorphone Hydrochloride tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home. Inform patients that leaving Oxymorphone Hydrochloride tablets unsecured can pose a deadly risk to others in the home *[see Warnings and Precautions (5.1, 5.3), Drug Abuse and Dependence (9.2)].*

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

Addiction, Abuse, and Misuse
Inform patients that the use of oxymorphone hydrochloride tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death. Instruct patients not to share Oxymorphone Hydrochloride tablets with others and to take steps to protect oxymorphone hydrochloride tablets from theft or misuse.

Life-Threatening Respiratory Depression
Inform patients of the risks of life-threatening respiratory depression, including emphasizing that the risk is greatest when starting oxymorphone hydrochloride tablets or when the dosage is increased, and that it can occur even at recommended dosages.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Warnings and Precautions (5.2)].*

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

Interactions with Benzodiazepines and Other CNS Depressants
Inform patients and caregivers that potentially fatal additive effects may occur if oxymorphone hydrochloride tablets is used with benzodiazepines or other CNS depressants, including alcohol, *inq*, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids (gabapentin or pregabalin), and other opioids, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.3); Drug Interactions (7)].*

Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, naloxone and naltrexone). Discuss the availability of an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdoses) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose.

Discuss with the patient the options for obtaining an opioid overdose reversal agent (e.g., prescription, pharmacy, clinic, community or mail order, patient assistance programs *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

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

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

Advise patients and caregivers:
• how to treat with the overdose reversal agent in the event of an opioid overdose
• to tell family and friends about the opioid overdose reversal agent, and to keep it in a place where family and friends can access it in an emergency
• to read the Medication Guide and the instructions for use that will come with their opioid overdose reversal agent. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Hyperalgesia and Allodynia
Inform patients and caregivers not to increase opioid dosage without first consulting a healthcare provider. Inform patients and caregivers that unexpected symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain *[see Warnings and Precautions (5.6), Adverse Reactions (6.2)]*.

Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions
Inform patients that anaphylaxis, angioedema, and other hypersensitivity reactions have occurred in patients taking oxymorphone hydrochloride tablets. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Warnings and Precautions (5.8), Adverse Reactions (6)].*

Serotonin Syndrome
Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications *[see Drug Interactions (7)]*.

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

Important Administration Instructions
Instruct patients how to properly take oxymorphone hydrochloride tablets exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression).
• Advise patients not to adjust the dose of oxymorphone hydrochloride tablets without consulting with a physician or other healthcare professional.

Important Discontinuation Instructions
In order to avoid developing withdrawal symptoms, instruct patients not to discontinue oxymorphone hydrochloride tablets without first discussing a tapering plan with the prescriber *[see Dosage and Administration (2.8)].*

Driving or Operating Heavy Machinery
Inform patients that oxymorphone hydrochloride tablets may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery, to a degree that is dependent on dose and other factors. Know how they will react to the medication *[see Warnings and Precautions (5.10)]*.

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

Adrenal Insufficiency
Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.8)]*.

Hypotension
Inform patients that oxymorphone hydrochloride tablets may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.9)]*.

Pregnancy
Neonatal Opioid Withdrawal Syndrome
Inform female patients of reproductive potential that use of oxymorphone hydrochloride tablets for an extended period of time during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.

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

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

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

Dispense with Medication Guide available at
https://www.aurobindousa.com/medication-guides/

Distributed by:
Aurobindo Pharma USA, Inc.
279 Princeton-Hightstown Road
East Windsor, NJ 08520

Revised: 12/2025

MEDICATION GUIDE

Medication Guide
Oxymorphone Hydrochloride (ox" i mor' fone hye" dron kloe' ide) Tablets, for oral use, CII

Oxymorphone Hydrochloride Tablets is:
● A strong prescription pain medicine that contains an opioid (narcotic) that is used to treat pain that is severe enough to require an opioid medicine, and for which other pain medicines do not treat your pain well enough or you cannot tolerate them.
● An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about Oxymorphone Hydrochloride Tablets:
Accidental ingestion of even one dose of Oxymorphone Hydrochloride Tablets can be life-threatening (overdose). When you first start taking oxymorphone hydrochloride tablets, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Ask your healthcare provider about medicines like naloxone or naltrexone that can be used to treat an overdose of opioid medicines.
● Taking oxymorphone hydrochloride tablets with other opioid medicines, benzodiazepines, gabapentinoids (gabapentin or pregabalin), alcohol, or other central nervous system depressants (including illicit drugs) may cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
● Never give anyone your oxymorphone hydrochloride tablets. They could die from taking it. Selling or giving away oxymorphone hydrochloride tablets is against the law.
● Store oxymorphone hydrochloride tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

Do not take Oxymorphone Hydrochloride Tablets if you have:
● a severe breathing problem including asthma or emphysema.
● a bowel blockage or have narrowing of the stomach or intestines.

Before taking Oxymorphone Hydrochloride Tablets, tell your healthcare provider if you have a history of:
● head injury, seizures
● problems urinating
● liver, kidney, thyroid problems
● pancreas or gallbladder problems
● abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems.

Tell your healthcare provider if you are:
● noticing your pain getting worse. If your pain gets worse after you take oxymorphone hydrochloride tablets, it may be a sign of a condition called opioid-induced hyperalgesia. Talk about this with your healthcare provider. Talk to your healthcare provider if the pain that you have increases, if you feel more sensitive to pain, or if you have new pain after taking oxymorphone hydrochloride tablets.
● **pregnant or planning to become pregnant.** Use of oxymorphone hydrochloride tablets for an extended period of time during pregnancy can result in withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
● **breastfeeding.** Oxymorphone hydrochloride tablets passes into breast milk and may harm your baby. Carefully observe infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Immediately seek medical care if these signs appear.
● living in a household where there are small children or someone who has abused street or prescription drugs
● taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking oxymorphone hydrochloride tablets with certain other medicines can cause serious side effects or death.

When taking Oxymorphone Hydrochloride Tablets:
● Do not change your dose. Take Oxymorphone Hydrochloride Tablets exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
● If you have (short-term) pain, you may only need to take oxymorphone hydrochloride tablets for a few days. You may have some oxymorphone hydrochloride tablets left over that you did not use. See disposal information at the bottom of this section for directions on how to safely throw away (dispose of) your unused oxymorphone hydrochloride tablets.
● Oxymorphone hydrochloride tablets should be taken on an empty stomach, at least one hour prior to or two hours after eating.
● Take your prescribed dose at the same time every day. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
● Call your healthcare provider if the dose you are taking does not control your pain.
● Talk to your healthcare provider before you stop taking oxymorphone hydrochloride or taking oxymorphone hydrochloride tablets without talking to your healthcare provider.
● Dispose of expired, unwanted, or unused oxymorphone hydrochloride tablets by flushing down the toilet if a drug take-back option is not readily available. If a drug take-back option is not available, you can dispose of oxymorphone hydrochloride tablets by mixing the product with dirt, cat litter, or coffee grounds; placing the mixture in a sealed plastic bag, and throwing the bag in your trash. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking Oxymorphone Hydrochloride Tablets DO NOT:
● Drive or operate heavy machinery, until you know how oxymorphone hydrochloride tablets affects you. Oxymorphone Hydrochloride Tablets can make you sleepy, dizzy, or lightheaded.
● Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Taking oxymorphone hydrochloride tablets during treatment with Oxymorphone Hydrochloride Tablets may cause you to overdose and die.

The possible side effects of Oxymorphone Hydrochloride Tablets:
● constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are bothersome.

Get emergency medical help or call 911 right away if you have:
● trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, throat, or tongue, severe itching, rash, or hives, fainting, seizures, 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 oxymorphone hydrochloride tablets. Call your doctor healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

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

Dispense with Medication Guide available at
https://www.aurobindousa.com/medication-guides/

Distributed by:
Aurobindo Pharma USA, Inc
279 Princeton-Hightstown Road
East Windsor, NJ 08520
Revised: 08/2025

PACKAGE LABEL-PRINCIPAL DISPLAY PANEL- Oxymorphone Hydrochloride Tablets 5mg (100 count bottle label)
Oxymorphone Hydrochloride Tablets CII
NDC 13107-103-01
5 mg (100 Tablets)

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL- Oxymorphone Hydrochloride Tablets 10mg (100 count bottle label)

Oxymorphone Hydrochloride Tablets C II
NDC 13107-104-01
10 mg (100 Tablets)

OXYMORPHONE HYDROCHLORIDE

oxymorphone hydrochloride tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:13107-105
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Oxymorphone Hydrochloride (UNII: 51XR0A8BZ2) (Oxymorphone - UNII:0E2693D50Z)	Oxymorphone Hydrochloride	5 mg

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

Product Characteristics

Color	Bluish (light-blue to blue)	**Score**	no score
Shape	ROUND (modified)	**Size**	8mm
Flavor		**Imprint Code**	105
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13107-105-01	30 in 1 BOTTLE, Type 0: Not a Combination Product	06/29/2018	
2	NDC:13107-105-05	500 in 1 BOTTLE, Type 0: Not a Combination Product	06/29/2018	
3	NDC:13107-105-10	1000 in 1 BOTTLE, Type 0: Not a Combination Product	06/29/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204408	06/29/2018	

OXYMORPHONE HYDROCHLORIDE

oxymorphone hydrochloride tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:13107-104
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Oxymorphone Hydrochloride (UNII: 51XR0A8BZ2) (Oxymorphone - UNII:0E2693D50Z)	Oxymorphone Hydrochloride	10 mg

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	
FD&C RED NO. 40 (UNII: WZB9127XOG)	

Product Characteristics

Color	ORANGE (Light Peach to Peach)	**Score**	no score
Shape	ROUND (modified)	**Size**	8mm
Flavor		**Imprint Code**	104
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13107-104-01	30 in 1 BOTTLE, Type 0: Not a Combination Product	06/29/2018	
2	NDC:13107-104-05	500 in 1 BOTTLE, Type 0: Not a Combination Product	06/29/2018	
3	NDC:13107-104-10	1000 in 1 BOTTLE, Type 0: Not a Combination Product	06/29/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204408	06/29/2018	

Labeler - Aurolife Pharma, LLC (079339401)

Establishment

Name	Address	ID/FEI	Business Operations
Aurolife Pharma, LLC		079339401	MANUFACTURE(13107-105, 13107-104)

Revised: 12/2020