930-04-2023
OXYMORPHONE HYDROCHLORIDE TABLETS CII

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 exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (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 for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.3, 7)**
- **Prolonged use of oxymorphone hydrochloride tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)**
- **To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.5)**
- **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. (5.3)**

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

Indications and Usage (1)
Dosage and Administration (2.1, 2.3)
Warnings and Precautions (5.6)

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

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

Limitations of Use:

Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration, reserve oxymorphone hydrochloride tablets for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or opioid combination products):

- Have not been tolerated, or are not expected to be tolerated, (1)
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia (1)

Oxymorphone hydrochloride tablets should not be used for an extended period of time unless the pain remains severe enough to require an opioid analgesic and for which alternative treatment options continue to be inadequate.

----------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 of time consistent with individual patient treatment goals. 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 are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks. (2.1, 5)
- 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)
- There is variability in the opioid analgesic dose and duration needed to adequately manage pain due both to the cause of pain and to individual patient factors. 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 dosage 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 four to six hours as needed for pain, at the lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of oxymorphone hydrochloride tablets. (2.3, 5)
- Oxymorphone hydrochloride tablets should be taken on an empty stomach, at least one hour prior to or two hours after eating. (2.1)
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with oxymorphone hydrochloride tablets. Consider prescribing naloxone based on the patient's risk factors for overdose (2.2, 5.1, 5.2, 5.3).
- Conversion to oxymorphone hydrochloride tablets: Follow recommendations for conversion from other opioids or parenteral oxymorphone. (2.3)
- Do not abruptly discontinue oxymorphone hydrochloride tablets in a physically dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.9)
- Mild Hepatic Impairment: Initiate treatment with 5 mg and titrate slowly. Monitor for signs of respiratory and central nervous system depression. (2.4)
- Renal Impairment: Initiate treatment with 5 mg and titrate slowly. Monitor for signs of respiratory and central nervous system depression. (2.5)
- Geriatric Patients: Initiate dosing with 5 mg, titrate slowly, and monitor for signs of respiratory and central nervous system depression. (2.6)
- CNS Depressants: Initiate treatment with 1/3 to 1/2 the recommended starting dose, consider using a lower dosage of the concomitant CNS depressant, and monitor closely. (2.7, 5.7, 7)

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

Tablets: 5 mg and 10 mg. (3)

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

- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to 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 opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safety switching the patient to a different opioid moiety). (5.6)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Regularly evaluate closely, particularly during initiation and titration. (5.2)
- Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions: If symptoms occur, stop administration immediately, discontinue permanently, and do not rechallenge with any oxymorphone formulation. (5.8)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.9)
- Severe Hypotension: Regularly evaluate during dosage initiation and titration. Avoid use of oxymorphone hydrochloride tablets in patients with circulatory shock. (5.10)
- 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. (5.11)

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Camber Pharmaceuticals Inc. at 1-866-495-8330 or FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.

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

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue oxymorphone hydrochloride tablets if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with oxymorphone hydrochloride tablets because they may reduce analgesic effect of oxymorphone hydrochloride tablets or precipitate withdrawal symptoms. (7)
- Monoamine oxidase inhibitors (MAOIs): Can potentiate the effects of oxymorphone. Avoid concomitant use in patients receiving MAOIs 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.

Revision: 04/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

Addiction, Abuse, and Misuse

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

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of 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 of 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 benzodiazepines 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

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

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

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

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 (5.3)]*.

1 INDICATIONS AND USAGE

Oxymorphone hydrochloride tablets are 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 with opioids, which can occur at any dosage or duration *[see Warnings and Precautions (5.1)]*, reserve oxymorphone hydrochloride tablets for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or opioid combination products)

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

Oxymorphone hydrochloride tablets should not be used for an extended period of time unless the pain remains severe enough to require an opioid analgesic and for which treatment options continue to be inadequate.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

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 are 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 due both to the cause of pain and to individual patient factors. 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 dosage increases with oxymorphone hydrochloride tablets. Consider this risk when selecting an initial dose and when making dose adjustments *[see Warnings and Precautions (5)]*.

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)]*.

To avoid medication errors, prescribers and pharmacists must be aware that 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)]*.

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

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

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

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

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

2.3 Initial Dosage

Use of Oxymorphone Hydrochloride Tablets as the First Opioid Analgesic

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 analgesia. Titrate the dose based upon the individual patient's response to their initial dose of oxymorphone hydrochloride tablets.

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, a conservative approach is advised when determining the total daily dosage 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, every 4-6 hours. The initial dose of oxymorphone hydrochloride tablets 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 tablets absolute oral 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.

2.4 Dosage Modifications in Patients with Mild Hepatic Impairment

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

Use oxymorphone hydrochloride tablets with caution in patients with mild hepatic impairment, 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 (5.2) and Clinical Pharmacology (12.3)]*.

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 (5.2) 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 with 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 or 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 and the relative incidence of adverse reaction as well as reassessing for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the oxymorphone hydrochloride tablets dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.9 Safe Reduction or Discontinuation of Oxymorphone Hydrochloride Tablets

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

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

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on 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 proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

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

When managing patients taking opioid analgesics, particularly those who have been treated for an extended period of time, and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.14), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets 5 mg: White to off white round flat tablets de-bossed with **'T 277'** on one side and plain on the other side.

Tablets 10 mg: Pink round flat tablets de-bossed with **'T 278'** 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 (5.7)]*
- 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 (5.8), Adverse Reactions (6)]*
- Moderate or severe hepatic impairment *[see Warnings and Precautions (5.16)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

Oxymorphone hydrochloride tablet 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 if the drug is misused or abused.

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 potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as 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 for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

Opioids are sought for non-medical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing 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 proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 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 death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of 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 (2.9)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with oxymorphone hydrochloride tablets. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered *[see Patient Counseling Information (17)]*.

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

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

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

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

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

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

5.4 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 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 Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient prescriber agreements that reinforce patient-prescriber responsibilities.

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

5.6 Opioid-Induced Hyperalgesia and Allodynia

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

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safety switching the patient to a different opioid moiety) *[see Dosage and Administration (2.2); Warnings and Precautions (5.5)]*.

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 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 (5.2)]*.

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

Regularly evaluate patients, particularly when initiating and titrating oxymorphone hydrochloride tablets and when oxymorphone hydrochloride tablets are given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (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 occurred in patients treated with 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 immediately, discontinue oxymorphone hydrochloride tablets permanently, and do 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 testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.10 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 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 CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), oxymorphone hydrochloride tablets may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with 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 Use in Patients with Gastrointestinal Conditions

Oxymorphone hydrochloride tablets are 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.

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 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 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 are 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 (5.4)]*
- 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)]*

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 postoperative 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 postoperative pain (N=557).

Table 1: Adverse Reactions Reported in Placebo-Controlled Trials

MedDRA Preferred Term	Oxymorphone Hydrochloride Tablets (N=557)	Placebo (N=270)
Nausea	19%	12%
Pyrexia	14%	8%
Somnolence	9%	2%
Vomiting	9%	7%
Pruritus	8%	4%
Headache	7%	4%
Dizziness (Excluding Vertigo)	7%	2%
Constipation	4%	1%
Confusion	3%	<1%

The **common** (≥1% - <10%) adverse drug reactions reported at least once by patients treated with oxymorphone hydrochloride tablets in the clinical trials organized by MedDRA's (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: anxiety and sedation

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, fatigue, depression, clamminess, flushing, hot flashes, dehydration, dermatitis, dyspepsia, 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, vision 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. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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)]*

7 DRUG INTERACTIONS

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

Table 2: 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 prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2, 2.7), Warnings and Precautions (5.1, 5.2, 5.3)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue oxymorphone hydrochloride tablets immediately 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 (5.2)]*. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.
Intervention:	The use of oxymorphone hydrochloride tablets is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of 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 muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.3)]*.
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 for diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Evaluate patients for signs of urinary retention or reduced gastric motility when oxymorphone hydrochloride tablets is used concomitantly with anticholinergic drugs.
Cimetidine	
Clinical Impact:	Cimetidine can potentiate opioid-induced respiratory depression.
Intervention:	Evaluate patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of oxymorphone hydrochloride tablets and/or cimetidine as necessary.

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 and through lactation at doses 2.4 and 12 times the human daily dose of 20 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 4.9 and 48.8 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 can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

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

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Oxymorphone hydrochloride tablets is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including oxymorphone

hydrochloride tablets, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

Pregnant rats were treated with 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, 25, or 50 mg/kg/day (9.8, 24.4, or 48.8 times the HDD based on body surface area, respectively). Decreased mean fetal weights were noted at 48.8 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 1, 5, 10, or 25 mg/kg/day (0.5, 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 the first week of life, reduced pup birth weight, and reduced postnatal weight gain 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 cranioschisis) were noted following subcutaneous administration of 153 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 or animal 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

Monitor 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.

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 effective starting doses in adults. In addition, pharmacokinetic results demonstrated 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, 31% 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, confusion, and nausea. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of 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 (5.7)]*.

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 monitor 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 is contraindicated for patients with moderate and severe hepatic impairment *[see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.16), 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 (12.3)]*. 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 (12.3)]*.

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 health care 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 overdosage, 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 central nervous-system 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 re-evaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of oxymorphone hydrochloride tablets abuse include those with a history of prolonged use of 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 contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among people who abuse drugs and people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

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

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

Risks Specific to Abuse of Oxymorphone Hydrochloride Tablets

Abuse of oxymorphone hydrochloride tablets poses a risk of overdose and death. This risk is increased with concurrent abuse of oxymorphone hydrochloride tablets with alcohol and other central nervous system depressants.

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

9.3 Dependence

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

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

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

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

Do not abruptly discontinue 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 serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing oxymorphone hydrochloride tablets, gradually taper the dosage using a patient-specific plan that considers the following: the dose of oxymorphone hydrochloride tablets the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for an extended period of time at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Dosage and Administration (2.9), Warnings and Precautions (5.14)]*.

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, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

Treatment of Overdose

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

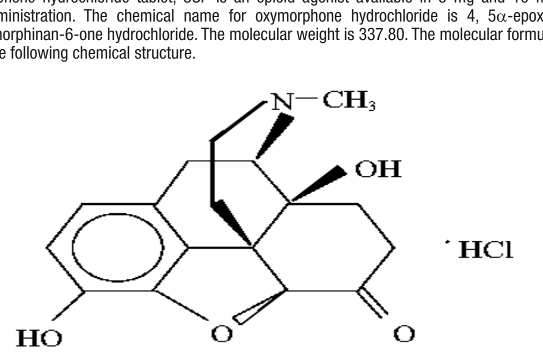
Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to opioid overdose, administer an opioid antagonist.

Because the duration of 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 antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

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

11 DESCRIPTION

Oxymorphone hydrochloride tablet, USP is an opioid agonist available in 5 mg and 10 mg tablet strengths for oral administration. The chemical name for oxymorphone hydrochloride is 4, 5α-epoxy-3, 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, USP is white to off white powder, which is soluble in water, sparingly soluble in alcohol and ether.

The inactive ingredients in oxymorphone hydrochloride tablets, USP include: lactose anhydrous, magnesium stearate, microcrystalline cellulose and pregelatinized starch. In addition, the 10 mg tablets contain D&C red No. 30 talc lake.

USP Dissolution Test Pending.

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 origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

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 may be increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

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

Effects on the Immune System

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

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with extended-release agonist 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, 2.3)]*.

Concentration–Adverse Reaction Relationships

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 tablets 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 3).

Table 3: Mean (±SD) Oxymorphone Hydrochloride Tablets Pharmacokinetic Parameters

Regimen	Dosage	C_{max} (ng/mL)	AUC (ng·hr/mL)	$T_{1/2}$ (hr)
Single Dose	5 mg 10 mg 20 mg	1.10±0.55 1.93±0.75 4.39±1.72	4.48±2.07 9.10±3.40 20.07±5.80	7.25±4.40 7.78±3.58 9.43±3.36
Multiple Dose[a]	5 mg 10 mg 20 mg	1.73±0.62 3.51±0.91 7.33±2.93	4.63±1.49 10.19±3.34 21.10±7.59	NA NA NA

NA = not applicable
[a] Results after 5 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

Formal 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%.

Elimination

Half-life ranges from approximately 9-11 hours after a single oral dose (5-40 mg).

Metabolism

Oxymorphone is highly metabolized, principally in the liver, and undergoes reduction or conjugation with glucuronic acid to form both active and inactive products. 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 have analgesic bioactivity. The mean plasma 6-OH-oxymorphone AUC is approximately 70% 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, 33% 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 plasma levels 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_{ss} and C_{max} values than male subjects. However, sex differences were not observed when AUC_{ss} 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 markedly increased in patients with moderate to severe liver disease. The effect of 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 1.6-fold in patients with mild hepatic impairment and by 3.7-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 65% in oxymorphone bioavailability was observed in mild (creatinine clearance 51-80 mL/min; n=8), moderate (creatinine clearance 30-50 mL/min; n=8), and severe (creatinine clearance <30 mL/min; n=8) patients, respectively, compared to healthy controls.

Drug Interactions Studies

In vitro studies revealed little to no 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 μM. An inhibition of CYP 3A4 activity occurred at oxymorphone concentrations ≥150 μM. Therefore, 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 ER 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 has 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 extended-release oxymorphone tablets in healthy, fasted volunteers. Following 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 31% and up to 260% 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 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 increase in micronucleated polychromatic erythrocytes occurred in mice given doses of ≥250 mg/kg and in rats given doses of 20 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 produce a marked, rapid increase in 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, 4.9, or 12.2 times the human daily dose of 20 mg/day based on body surface area, 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 evaluated the doses of 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 0-4 categorical, compared to placebo. Oxymorphone hydrochloride tablets 10 mg provided greater analgesia as compared to 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 postoperative 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 acute pain following abdominal surgery. In this study, patients were dosed every 4 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 0-100 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, USP are supplied as follows:

5 mg Tablet:

White to off white round flat tablets de-bossed with **'T 277'** on one side and plain on the other side.

Bottles of 100 tablets with child-resistant closure NDC 31722-929-01

10 mg Tablet:

Pink round flat tablets de-bossed with **'T 278'** on one side and plain on the other side.

Bottles of 100 tablets with child-resistant closure NDC 31722-930-01

Store at 20°C - 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 *[see Warnings and Precautions (5.1, 5.2), Drug Abuse and Dependence (9.2)]*. Inform patients that leaving oxymorphone hydrochloride tablets unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused oxymorphone hydrochloride 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 *[see Warnings and Precautions (5.1)].* 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 risk of life-threatening respiratory depression, including information 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 tablet is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.3), Drug Interactions (7)].*

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with oxymorphone hydrochloride tablets. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) *[see Dosage and Administration ((2.2), Warnings and Precautions (5.2)]*.

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

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

If naloxone is prescribed, also advise patients and caregivers:

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

Hyperalgesia and Allodynia

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

Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions

Inform patients that anaphylaxis, angioedema, and other hypersensitivity reactions have been reported with ingredients contained in 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 (2.9)]*.

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. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.15)]*.

Constipation

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

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 (5.9)].*

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 (5.10)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

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

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that 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

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

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2)].*

Manufactured by:
Ascent Pharmaceuticals, Inc.
Central Islip, NY 11722

Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854

Revised: 04/23

Medication Guide
Oxymorphone hydrochloride (OX-i-MOR-fone HYE-droe-KLOR-ide) tablets, for oral use, CII

Oxymorphone hydrochloride tablets are:
- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage short-term (acute) pain when other pain treatments such as non-opioid 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:
- **Get emergency help or call 911 right away if you take too much oxymorphone hydrochloride tablets (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. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking oxymorphone hydrochloride tablets with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your 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:
- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

taking oxymorphone hydrochloride tablets, tell your healthcare provider if you have a history of:
- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems.

Tell your healthcare provider if you are:
- **Are pregnant or planning to become pregnant.** Use of oxymorphone hydrochloride tablets for an extended period of time during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **Notice your pain getting worse.** If your pain gets worse after you take oxymorphone hydrochloride tablets, do not take more of oxymorphone hydrochloride tablets without first talking to your doctor. Talk to your doctor if the pain you have increases, if you feel more sensitive to pain, or if you have new pain after taking oxymorphone hydrochloride tablets.
- **breastfeeding.** Oxymorphone hydrochloride tablets passes into breast milk and may harm your baby.
- 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 that could lead to 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.
- For acute (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 dispose of 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.
- If you have been taking oxymorphone hydrochloride tablets regularly, do not stop taking oxymorphone hydrochloride tablets without talking to your healthcare provider.
- Dispose of expired, unwanted, or unused oxymorphone hydrochloride tablets by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking 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. Using products containing alcohol 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 severe.

Get emergency medical help or call 911 right away if you have:
- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat or hands, hives, itching, rash, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of oxymorphone hydrochloride tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or call Camber Pharmaceuticals, Inc. at 1-866-495-8330. **For more information go to dailymed.nlm.nih.gov**

Medication Guide available at http://camberpharma.com/medication-guides

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