HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OPANA® ER safely and effectively. See full prescribing information for OPANA® ER.

OPANA® ER (oxymorphone hydrochloride) extended-release tablets, for oral use, CII

Initial U.S. Approval: 1959

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

***See full prescribing information for complete boxed warning*.**

- **OPANA ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow OPANA ER tablets whole to avoid exposure to a potentially fatal dose of oxymorphone. (5.2)**
- **Accidental ingestion of OPANA ER, especially by children, can result in fatal overdose of oxymorphone. (5.2)**
- **Prolonged use of OPANA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.3).**
- **Instruct patients not to consume alcohol or any product containing alcohol while taking OPANA ER because co-ingestion can result in fatal plasma oxymorphone levels. (5.4)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)**

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

Boxed Warning	12/2016
Dosage and Administration (2)	12/2016
Contraindications (4)	12/2016
Warnings and Precautions (5)	12/2016

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

OPANA ER is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve OPANA ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- OPANA ER is not indicated as an as-needed (prn) analgesic. (1)

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

- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Administer on an empty stomach, at least 1 hour prior to or 2 hours after eating. (2.1)
- OPANA ER tablets should be taken one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. (2.1, 17)
- For opioid-naïve and opioid non-tolerant patients, initiate treatment with 5 mg tablets orally every 12 hours. (2.2)
- To convert to OPANA ER from another opioid, use available conversion factors to obtain estimated dose. (2.2)
- Dose can be increased every 3 to 7 days, using increments of 5 to 10 mg every 12 hours (i.e., 10 to 20 mg per day). (2.3)
- Do not abruptly discontinue OPANA ER in a physically dependent patient. (2.4, 5.14)
- Mild Hepatic Impairment: For opioid-naïve patients, initiate treatment with 5 mg and titrate slowly. For patients on prior opioid therapy, reduce starting dose by 50% and titrate slowly. Monitor for signs of respiratory and central nervous system depression. (2.5)
- Renal Impairment: For opioid-naïve patients, initiate treatment with 5 mg and titrate slowly. For patients on prior opioid therapy, reduce starting dose by 50% and titrate slowly. Monitor for signs of respiratory and central nervous system depression. (2.6)
- Geriatric Patients: Initiate dosing with 5 mg, titrate slowly, and monitor for signs of respiratory and central nervous system depression. (2.7)

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

Extended-release tablets: 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg

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

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment (4)
- Hypersensitivity to oxymorphone (4)
- Moderate or severe hepatic impairment (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)

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

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.5, 5.6)
- Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions: If symptoms occur, stop administration immediately, discontinue permanently, and do not rechallenge with any oxymorphone formulation. (5.6)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.7)
- Severe Hypotension: Monitor during dose initiation and titration. Avoid use of OPANA ER in patients with circulatory shock. (5.9)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of OPANA ER in patients with impaired consciousness or coma. (5.10)
- Difficulty in Swallowing: Use with caution in patients who have difficulty in swallowing or have underlying GI disorders that may predispose them to obstruction. (5.11)

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

Adverse reactions in ≥2% of patients in placebo-controlled trials: nausea, constipation, dizziness, somnolence, vomiting, pruritus, headache, sweating increased, dry mouth, sedation, diarrhea, insomnia, fatigue, appetite decreased, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Endo Pharmaceuticals Inc. at 1-800-462-3636 or FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.

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

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue OPANA ER if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with OPANA ER because they may reduce analgesic effect of OPANA ER 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 treatment with an MAOI. (7)

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

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not Recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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

FULL PRESCRIBING INFORMATION

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

Addiction, Abuse, and Misuse

OPANA ER 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 OPANA ER, and monitor 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 OPANA ER. Monitor for respiratory depression, especially during initiation of OPANA ER or following a dose increase. Instruct patients to swallow OPANA ER tablets whole; crushing, chewing, or dissolving OPANA ER tablets can cause rapid release and absorption of a potentially fatal dose of oxymorphone *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

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

Neonatal Opioid Withdrawal Syndrome

Prolonged use of OPANA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Interaction with Alcohol

Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking OPANA ER. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone *[see Warnings and Precautions (5.4)*

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 *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of OPANA ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

1 INDICATIONS AND USAGE

OPANA ER is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations *[see Warnings and Precautions (5.1)]*, reserve OPANA ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- OPANA ER is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

OPANA ER should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5.1)]*.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with OPANA ER and adjust the dosage accordingly *[see Warnings and Precautions (5.2)]*.

Instruct patients to swallow OPANA ER tablets whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17)]*. Crushing, chewing, or dissolving OPANA ER tablets will result in uncontrolled delivery of oxymorphone and can lead to overdose or death *[see Warnings and Precautions (5.2)]*.

Administer on an empty stomach, at least 1 hour prior to or 2 hours after eating.

OPANA ER is administered orally every 12 hours.

2.2 Initial Dosage

Use of OPANA ER as the First Opioid Analgesic

Initiate treatment with OPANA ER with the 5 mg tablet orally every 12-hours.

Use of OPANA ER in Patients who are not Opioid Tolerant

The starting dose for patients who are not opioid tolerant is OPANA ER 5 mg orally every 12 hours.

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

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression.

Conversion from OPANA to OPANA ER

Patients receiving OPANA may be converted to OPANA ER by administering half the patient's total daily oral OPANA dose as OPANA ER, every 12 hours.

Conversion from Parenteral Oxymorphone to OPANA ER

The absolute oral bioavailability of OPANA ER is approximately 10%. Convert patients receiving parenteral oxymorphone to OPANA ER by administering 10 times the patient's total daily parenteral oxymorphone dose as OPANA ER in two equally divided doses (e.g., [IV dose x 10] divided by 2). Due to patient variability with regards to opioid analgesic response, upon conversion monitor patients closely to evaluate for adequate analgesia and side effects.

Conversion from Other Oral Opioids to OPANA ER

Discontinue all other around-the-clock opioid drugs when OPANA ER therapy is initiated.

While there are useful tables of opioid equivalents readily available, there is substantial inter- patient variability in the relative potency of different opioid drugs and products. As such, it is preferable to underestimate a patient’s 24-hour oral oxymorphone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral oxymorphone requirements which could result in adverse reactions. In an OPANA ER clinical trial with an open-label titration period, patients were converted from their prior opioid to OPANA ER using Table 1 as a guide for the initial OPANA ER dose.

Consider the following when using the information in Table 1:

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

CONVERSION FACTORS TO OPANA ER	
Prior Oral Opioid	Approximate Oral Conversion Factor
Oxymorphone	1
Hydrocodone	0.5
Oxycodone	0.5
Methadone	0.5
Morphine	0.333

To calculate the estimated OPANA ER dose using Table 1:

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

Always round the dose down, if necessary, to the appropriate OPANA ER strength(s) available.

Example conversion from a single opioid to OPANA ER:

Step 1: Sum the total daily dose of the opioid oxycodone 20 mg BID

20 mg former opioid 2 times daily = 40 mg total daily dose of former opioid

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

40 mg total daily dose of former opioid x 0.5 mg Conversion Factor = 20 mg of oral oxymorphone daily

Step 3: Calculate the approximate starting dose of OPANA ER to be given every 12 hours. Round down, if necessary, to the appropriate OPANA ER TABLETS strengths available.

10 mg OPANA ER every 12 hours

Conversion from Methadone to OPANA ER

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

2.3 Titration and Maintenance of Therapy

Individually titrate OPANA ER to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OPANA ER to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, and misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.

If the level of pain increases, attempt to identify the source of increased pain, while adjusting the OPANA ER dose to decrease the level of pain. Because steady-state plasma concentrations are approximated within 3 days, OPANA ER dosage adjustments, preferably at increments of 5-10 mg every 12 hours, may be done every 3 to 7 days.

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

If unacceptable opioid-related adverse reactions are observed, the subsequent dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.4 Discontinuation of OPANA ER

When a patient no longer requires therapy with OPANA ER, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue OPANA ER *[see Warnings and Precautions (5.14), Drug Abuse and Dependence (9.3)]*.

2.5 Dosage Modification in Patients with Mild Hepatic Impairment

OPANA ER is contraindicated in patients with moderate or severe hepatic impairment.

In opioid-naïve patients with mild hepatic impairment, initiate treatment with the 5 mg dose. For patients on prior opioid therapy, start OPANA ER at 50% lower than the starting dose for a patient with normal hepatic function on prior opioids and titrate slowly. Monitor patients closely for signs of respiratory or central nervous system depression *[see Warnings and Precautions (5.2), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.6 Dosage Modification in Patients with Renal Impairment

In patients with creatinine clearance rates less than 50 mL/min, start OPANA ER in the opioid-naïve patient with the 5 mg dose. For patients on prior opioid therapy, start OPANA ER at 50% lower than the starting dose for a patient with normal renal function on prior opioids and titrate slowly. Monitor patients closely for signs of respiratory or central nervous system depression *[see Warnings and Precautions (5.2), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.7 Dosage Modification in Geriatric Patients

The steady-state plasma concentrations of oxymorphone are higher in elderly subjects than in young subjects. Initiate dosing with OPANA ER in patients 65 years of age and over using the 5 mg dose and monitor closely for signs of respiratory and central nervous system depression when initiating and titrating OPANA ER to adequate analgesia *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5) and Clinical Pharmacology (12.3)]*. For patients on prior opioid therapy, start OPANA ER at 50% lower than the starting dose for a younger patient on prior opioids and titrate slowly.

3 DOSAGE FORMS AND STRENGTHS

Extended Release Tablets 5 mg: pink, round, film-coated, biconcave extended-release tablet debossed with an "E" on one side and a "5" on the other side.

Extended Release Tablets 7.5 mg: gray, round, film-coated, biconcave extended-release tablet debossed with an "E" on one side and a "7 ½" on the other side.

Extended Release Tablets 10 mg: light orange, round, film-coated, biconcave extended-release tablet debossed with an "E" on one side and a "10" on the other side.

Extended Release Tablets 15 mg: white, round, film-coated, biconcave extended-release tablet debossed with an "E" on one side and a "15" on the other side.

Extended Release Tablets 20 mg: light green, round, film-coated, biconcave extended-release tablet debossed with an "E" on one side and a "20" on the other side.

Extended Release Tablets 30 mg: red, round, film-coated, biconcave extended-release tablet debossed with an "E" on one side and a "30" on the other side.

Extended Release Tablets 40 mg: light yellow to pale yellow, round, film-coated, biconcave extended-release tablet debossed with an "E" on one side and a "40" on the other side.

4 CONTRAINDICATIONS

OPANA ER is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.2)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.5)]*
- Hypersensitivity to oxymorphone, (e.g. anaphylaxis) *[see Warnings and Precautions (5.6), Adverse Reactions (6)]*
- Moderate and severe hepatic impairment *[see Warnings and Precautions (5.8), Clinical Pharmacology (12.3)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.11)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

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

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OPANA ER. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing OPANA ER, and monitor all patients receiving OPANA ER 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 OPANA ER, but use in such patients necessitates intensive counseling about the risks and proper use of OPANA ER along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of OPANA ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the oxymorphone and can result in overdose and death *[see Overdosage (10)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OPANA ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact 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 from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OPANA ER, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within 24-72 hours of initiating therapy with and following dose increases of OPANA ER.

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

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

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of OPANA ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

5.4 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 OPANA ER therapy. The co-ingestion of alcohol with OPANA ER 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 OPANA ER 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. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when OPANA ER is used with benzodiazepine 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) and Patient Counseling Information (17)]*.

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

The use of OPANA ER 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: OPANA ER-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 OPANA ER *[see Warnings and Precautions (5.2)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.2)]*.

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

5.6 Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions

Potentially life-threatening hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients treated with OPANA ER 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 OPANA ER immediately, discontinue OPANA ER 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)]*.

5.7 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.

5.8 Use in Patients with Hepatic Impairment

A study of OPANA ER in patients with hepatic disease indicated greater plasma concentrations than those with normal hepatic function *[see Clinical Pharmacology (12.3)]*. OPANA ER is contraindicated in patients with moderate or severe hepatic impairment. In patients with mild hepatic impairment reduce the starting dose to the lowest dose and monitor for signs of respiratory and central nervous system depression *[see Dosage and Administration (2.5)]*.

5.9 Severe Hypotension

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

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

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), OPANA ER 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 OPANA ER.

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

5.11 Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen

There have been post-marketing reports of difficulty in swallowing OPANA ER tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick or otherwise wet OPANA ER tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth.

There have been rare post-marketing reports of cases of intestinal obstruction, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen.

5.12 Risks of Use in Patients with Gastrointestinal Conditions

OPANA ER is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The oxymorphone in OPANA ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.13 Increased Risk of Seizures in Patients with Seizure Disorders

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

5.14 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) and partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including OPANA ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing OPANA ER, gradually taper the dosage *[see Dosage and Administration (2.4)]*. Do not abruptly discontinue OPANA ER.

5.15 Risks of Driving and Operating Machinery

OPANA ER 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 OPANA ER and know how they will react to the medication.

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 (5.3)]*
- Interactions with Benzodiazepines or Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Anaphylaxis and angioedema *[see Warnings and Precautions (5.6)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.7)]*
- Severe Hypotension *[see Warnings and Precautions (5.9)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.11, 5.12)]*
- Seizures *[see Warnings and Precautions (5.13)]*
- Withdrawal *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of oxymorphone hydrochloride extended-release tablets was evaluated in a total of 2011 patients in open-label and controlled clinical trials. The clinical trials enrolled of patients with moderate to severe chronic non-malignant pain, cancer pain, and post surgical pain. The most common serious adverse events reported with administration of oxymorphone hydrochloride extended-release tablets were chest pain, pneumonia and vomiting.

Tables 1 and 2 list the most frequently occurring adverse reactions (in at least 5% of patients) from the placebo-controlled trials in patients with low back pain.

Table 1:Treatment-Emergent Adverse Reactions Reported in ≥5% of Patients During the Open-Label Titration Period and Double-Blind Treatment Period by Preferred Term —Number (%) of Treated Patients (12-Week Study In Opioid-Naïve Patients with Low Back Pain)

	Open-Label Titration Period	Double-Blind Treatment Period	
	Oxymorphone Hydrochloride Extended-Release Tablets	Oxymorphone Hydrochloride Extended-Release Tablets	Placebo
Preferred Term	**(N = 325)**	**(N = 105)**	**(N = 100)**
Constipation	26%	7%	1%
Somnolence	19%	2%	0%
Nausea	18%	11%	9%
Dizziness	11%	5%	3%
Headache	11%	4%	2%
Pruritus	7%	3%	1%

Table 2: Treatment-Emergent Adverse Reactions Reported in ≥5% of Patients During the Open-Label Titration Period and Double-Blind Treatment Period by Preferred Term —Number (%) of Treated Patients (12-Week Study In Opioid-Experienced Patients with Low Back Pain)

	Open-Label Titration Period	Double-Blind Treatment Period	
	Oxymorphone Hydrochloride Extended-Release Tablets	Oxymorphone Hydrochloride Extended-Release Tablets	Placebo
Preferred Term	**(N = 250)**	**(N = 70)**	**(N = 72)**
Nausea	20%	3%	1%
Constipation	12%	6%	1%
Headache	12%	3%	0%
Somnolence	11%	3%	0%
Vomiting	9%	0%	1%
Pruritus	8%	0%	0%
Dizziness	6%	0%	0%

The following table lists adverse reactions that were reported in at least 2% of patients in placebo-controlled trials (N=5).

Table 3: Adverse Reactions Reported in Placebo-Controlled Clinical Trials with Incidence ≥2% in Patients Receiving Oxymorphone Hydrochloride Extended-Release Tablets

MedDRA Preferred Term	Oxymorphone Hydrochloride Extended-Release Tablets (N=1259)	Placebo (N=461)
Nausea	33%	13%
Constipation	28%	13%
Dizziness (Excl Vertigo)	18%	8%
Somnolence	17%	2%
Vomiting	16%	4%
Pruritus	15%	8%
Headache	12%	6%
Sweating increased	9%	9%
Dry mouth	6%	<1%
Sedation	6%	8%
Diarrhea	4%	6%
Insomnia	4%	2%
Fatigue	4%	1%
Appetite decreased	3%	<1%
Abdominal pain	3%	2%

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

Eye disorders: vision blurred

Gastrointestinal disorders: diarrhea, abdominal pain, dyspepsia

General disorders and administration site conditions**:** dry mouth, appetite decreased, fatigue, lethargy, weakness, pyrexia, dehydration, weight decreased, edema

Nervous system disorders: insomnia

Psychiatric disorders: anxiety, confusion, disorientation, restlessness, nervousness, depression

Respiratory, thoracic and mediastinal disorders: dyspnea

Vascular disorders: flushing and hypertension

Other less common adverse reactions known with opioid treatment that were seen <1% in the oxymorphone hydrochloride extended-release tablets trials include the following: Bradycardia, palpitation, syncope, tachycardia, postural hypotension, miosis, abdominal distention, ileus, hot flashes, allergic reactions, hypersensitivity, urticaria, oxygen saturation decreased, central nervous system depression, depressed level of consciousness, agitation, dysphoria, euphoric mood, hallucination, mental status changes, difficult micturition, urinary retention, hypoxia, respiratory depression, respiratory distress, clamminess, dermatitis, hypotension.

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 OPANA ER

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

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with OPANA ER

Table 4: Clinically Significant Drug Interactions with OPANA ER

Alcohol	
Clinical Impact:	The concomitant use of alcohol with OPANA ER 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 OPANA ER 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. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.4)]*.
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, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue OPANA ER 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), 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)]*.
Intervention:	The use of OPANA ER 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 OPANA ER 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:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of OPANA ER and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when OPANA ER is used concomitantly with anticholinergic drugs.
Cimetidine	
Clinical Impact:	Cimetidine can potentiate opioid-induced respiratory depression.
Intervention:	Monitor patients for respiratory depression when OPANA ER and cimetidine are used concurrently.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.3)]*. Available data with OPANA ER in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. 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 clinical recognized pregnancies is 2-4% and 14-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes may cause fetal-neonatal physical dependence and neonatal 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, including poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.3)]*.

Labor or delivery

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

8.2 Lactation

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).

Risk Summary

There is no information regarding the presence of oxymorphone in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with OPANA ER.

Clinical Considerations

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

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of OPANA ER in patients below the age of 18 years have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of oxymorphone hydrochloride extended-release tablets, 27% were 65 and over, while 9% 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. On average, age greater than 65 years was associated with an increase in oxymorphone AUC and C_{max}. Initiate dosing with OPANA ER in patients 65 years of age and over using the 5 mg dose and monitor closely for signs of respiratory and central nervous system depression when initiating and titrating OPANA ER. For patients on prior opioid therapy, start at 50% of the starting dose for a younger patient on prior opioids and titrate slowly.

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

Patients with mild hepatic impairment have an increase in oxymorphone bioavailability compared to the subjects with normal hepatic function. In opioid-naïve patients with mild hepatic impairment, initiate OPANA ER using the 5 mg dose and monitor closely for respiratory and central nervous system depression. OPANA ER is contraindicated for patients with moderate and severe hepatic impairment *[see Dosage and Administration (2.5), Contraindications (4), Warnings and Precautions (5.8), and, Clinical Pharmacology (12.3)]*. For patients on prior opioid therapy, start at the 50% of the dose for that a patient with normal hepatic function on prior opioids and titrate slowly.

8.7 Renal Impairment

Patients with moderate to severe renal impairment were shown to have an increase in oxymorphone compared to the subjects with normal renal function *[see Clinical Pharmacology (12.3)]*. Start opioid-naïve patients with the 5 mg dose of OPANA ER and titrate slowly while closely monitoring for respiratory and central nervous system depression *[see Dosage and Administration (2.6)]*. For patients on prior opioid therapy, start at 50% of the dose for a patient with normal renal function on prior opioids and titrate slowly.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OPANA ER contains oxymorphone, a Schedule II controlled substance.

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

9.2 Abuse

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

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

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

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

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

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

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

OPANA ER, 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.

<u>Risks Specific to Abuse of OPANA ER</u>

OPANA ER is for oral use only. Abuse of OPANA ER poses a risk of overdose and death. This risk is increased with concurrent abuse of OPANA ER with alcohol and other substances. Taking cut, broken, chewed, crushed, or dissolved OPANA ER enhances drug release and increases the risk of over dose and death.

With parenteral abuse, cases of thrombotic microangiopathy (a condition characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia) have been reported; many cases resulted in hospitalization and treatment with plasmapheresis. 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 chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

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

OPANA ER should not be abruptly discontinued [*see Dosage and Administration (2.3)]*. If OPANA ER is abruptly discontinued in a physically-dependent patient, withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: 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.

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 (8.2)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with OPANA ER can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

Treatment of Overdose

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

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose.

For clinically significant respiratory or circulatory depression secondary to oxymorphone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxymorphone overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of oxymorphone in OPANA ER, carefully monitor the patient until spontaneous respiration is reliably reestablished. OPANA ER will continue to release oxymorphone and add to the oxymorphone load for 24 hour to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed in 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

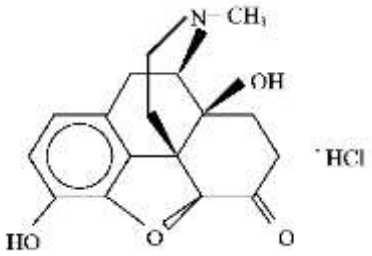
OPANA ER extended-release tablets are for oral use and contain oxymorphone, an opioid agonist. OPANA ER extended-release tablets are supplied in 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg tablet strengths for oral administration. The tablet strength describes the amount of oxymorphone hydrochloride per tablet.

The tablets contain the following inactive ingredients: hypromellose, polyethylene oxide, polyethylene glycol, α-tocopherol, citric acid, polyvinyl alcohol, titanium dioxide, macrogol and talc.

In addition, the 5 mg, 7.5 mg and 30 mg tablets contain iron oxide red. The 7.5 mg tablets contain iron oxide black, and iron oxide yellow. The 10 mg tablets contain FD&C yellow No. 6. The 20 mg tablets contain FD&C blue No. 1, FD&C yellow No. 6, and D&C yellow No. 10. The 40 mg tablets contain FD&C yellow No. 6, and D&C yellow No. 10.

The chemical name of oxymorphone hydrochloride is 4, 5α -epoxy-3, 14-dihydroxy-17-methylmorphinan-6-one hydrochloride, a white or slightly off-white, odorless powder, which is sparingly soluble in alcohol and ether, but freely soluble in water. The molecular weight of oxymorphone hydrochloride is 337.80. The pKa1 and pKa2 of oxymorphone at 37°C are 8.17 and 9.54, respectively. The octanol/aqueous partition coefficient at 37°C and pH 7.4 is 0.98.

The structural formula for oxymorphone hydrochloride is as follows:



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

12.2 Pharmacodynamics

CNS Depressant/Alcohol Interaction

Additive pharmacodynamic effects may be expected when OPANA ER is used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

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 on Other Smooth Muscle

Oxymorphone causes a reduction in motility and is associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Oxymorphone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Release of histamine can occur and may contribute to opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include, pruritus, flushing, red eyes, 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.

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

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *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 plasma concentration of oxymorphone varies widely among patients, especially among patients who have been previously treated with agonist opioids. The minimum effective analgesic concentration of oxymorphone for any individual patient may increase over time due to an increase in pain, development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.2)]*.

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, 2.2, 2.3)]*.

12.3 Pharmacokinetics

Absorption

The absolute oral bioavailability of oxymorphone is approximately 10%.

Steady-state levels are achieved after three days of multiple dose administration. Under both single-dose and steady-state conditions, dose proportionality has been established for the 5 mg, 10 mg, 20 mg, and 40 mg doses of oxymorphone hydrochloride extended-release tablets, for both peak plasma levels (C_{max}) and extent of absorption (AUC) (see Table 4).

Table 4: Mean (±SD) Oxymorphone Hydrochloride Extended-Release Tablets Pharmacokinetic Parameters

Regimen	Dosage	C_{max} (ng/mL)	$AUC_{0\text{-}12h}$ (ng·hr/mL)	$T_{½}$ (hr)
Single Dose	5 mg	0.27±0.13	4.54±2.04	11.30±10.81
	10 mg	0.65±0.29	8.94±4.16	9.83±5.68
	20 mg	1.21±0.77	17.81±7.22	9.89±3.21
	40 mg	2.59±1.65	37.90±16.20	9.35±2.94
Multiple Dose[a]	5 mg	0.70±0.55	5.60±3.87	NA
	10 mg	1.24±0.56	9.77±3.52	NA
	20 mg	2.54±1.35	19.28±8.32	NA
	40 mg	4.47±1.91	36.98±13.53	NA

NA = not applicable
[a] Results after 5 days of q12h dosing.

Food Effect

Two studies examined the effect of food on the bioavailability of single doses of 20 and 40 mg of oxymorphone hydrochloride extended-release tablets in healthy volunteers. In both studies, after the administration of oxymorphone hydrochloride extended-release tablets, the C_{max} was increased by approximately 50% in fed subjects compared to fasted subjects. A similar increase in C_{max} was also observed with oxymorphone solution.

The AUC was unchanged in one study and increased by approximately 18% in the other study in fed subjects following the administration of oxymorphone hydrochloride extended-release tablets. Examination of the AUC suggests that most of the difference between fed and fasting conditions occurs in the first four hours after dose administration. After oral dosing with a single dose of 40 mg, a peak oxymorphone plasma level of 2.8 ng/ml is achieved at 1hour in fasted subjects and a peak of 4.25 ng/ml is achieved at 2 hours in fed subjects and that beyond the 12 hour time point, there is very little difference in the curves. As a result, OPANA ER should be dosed at least one hour prior to or two hours after eating *[see Dosage and Administration (2.1, 2.2)]*.

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

Metabolism

Oxymorphone is highly metabolized, principally in the liver, and undergoes reduction or conjugation with glucuronic acid to form both active and inactive metabolites. 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 less than 1% 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

Geriatric Patients

The steady-state plasma concentrations of oxymorphone, 6-OH-oxymorphone, and oxymorphone-3-glucuronide are approximately 40% higher in elderly subjects (≥ 65 years of age) than in young subjects (18 to 40 years of age). On average, age greater than 65 years was associated with a 1.4-fold increase in oxymorphone AUC and a 1.5-fold increase in C_{max}. This observation does not appear related to a difference in body weight, metabolism, or excretion of oxymorphone *[see Use in Specific Populations (8.5)]*.

Sex

The effect of sex was evaluated following single- and multiple-doses of oxymorphone hydrochloride extended-release tablets in male and female adult volunteers. 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 bioavailability of orally administered oxymorphone is markedly increased in patients with moderate to severe liver disease. The disposition of oxymorphone was compared in six patients with mild, five 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

Data from a pharmacokinetic study involving 24 patients with renal dysfunction show an increase of 26%, 57%, and 65% in oxymorphone bioavailability 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 Interaction Studies

Alcohol Interaction

An *in vivo* study of the effect of alcohol (40%, 20%, 4% and 0%) on the bioavailability of a single dose of 40 mg of oxymorphone hydrochloride extended-release tablets in healthy, fasted volunteers demonstrated a highly variable effect on C_{max} with concomitant administration of alcohol and oxymorphone hydrochloride extended-release tablets. The change in C_{max} ranged from a decrease of 50% to an increase of 270% across all conditions studied. Following 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. Following the concomitant administration of 240 mL of 4 % ethanol, the C_{max} increased 7% on average and by as much as 110% for individual subjects. After oral dosing with a single dose of 40 mg in fasted subjects, the mean peak oxymorphone plasma level is 2.4 ng/mL and the median T_{max} is 2 hours. Following co-administration of oxymorphone hydrochloride extended-release tablets and alcohol (240 mL of 40% ethanol) in fasted subjects, the mean peak oxymorphone level is 3.9 ng/mL and the median T_{max} is 1.5 hours (range 0.75 – 6 hours). The oxymorphone mean AUC was 13% higher after co-administration of 240 mL of 40% alcohol. The AUC was essentially unaffected in subjects following the co-administration of oxymorphone hydrochloride extended-release tablets and ethanol (240 mL of 20% or 4% ethanol).

I*n vitro* studies have demonstrated that oxymorphone hydrochloride extended-release tablets does not release oxymorphone more rapidly in 500 mL of 0.1N HCl solutions containing ethanol (4%, 20%, and 40%).

Instruct patients to avoid use of alcohol when taking OPANA ER.

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 ≤15.1 μg/mL. An inhibition of CYP3A4 activity occurred at oxymorphone concentrations ≥45.3 μg/mL. 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 extended-release tablets 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.

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 ≥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 efficacy and safety of oxymorphone hydrochloride extended-release tablets have been evaluated in double-blind, controlled clinical trials in opioid-naïve and opioid-experienced patients with moderate to severe pain including low back pain.

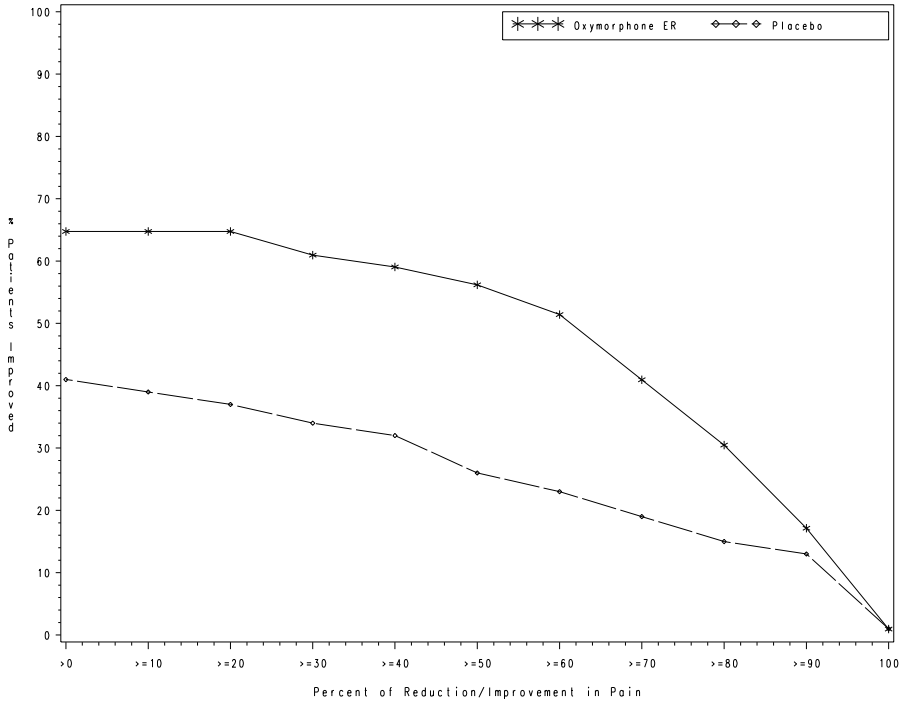
12-Week Study in Opioid-Naïve Patients with Low Back Pain

Patients with chronic low back pain who were suboptimally responsive to their non-opioid therapy entered a 4-week, open-label dose titration phase. Patients initiated therapy with two days of treatment with oxymorphone hydrochloride extended-release tablets 5 mg, every 12 hours. Thereafter, patients were titrated to a stabilized dose, at increments of 5 to 10 mg every 12 hours every 3 to 7 days. Of the patients who were able to stabilize within the Open-Label Titration Period, the mean±SD VAS score at Screening was 69.4±11.8 mm and at Baseline (beginning of Double-Blind Period) were 18.5±11.2 mm and 19.3±11.3 mm for the oxymorphone ER and placebo groups, respectively. Sixty three percent of the patients enrolled were able to titrate to a tolerable dose and were randomized into a 12-week double-blind treatment phase with placebo or their stabilized dose of oxymorphone hydrochloride extended-release tablets. The mean±SD stabilized doses were 39.2±26.4 mg and 40.9±25.3 mg for the oxymorphone hydrochloride extended-release tablets and placebo groups, respectively; total daily doses ranged from 10 to 140 mg. During the first 4 days of double-blind treatment patients were allowed an unlimited number of OPANA, an immediate-release (IR) formulation of oxymorphone, 5 mg tablets, every 4-6 hours as supplemental analgesia; thereafter the number of OPANA was limited to two tablets per day. This served as a tapering method to minimize opioid withdrawal symptoms in placebo patients. Sixty-eight percent of patients treated with oxymorphone hydrochloride extended-release tablets completed the 12-week treatment compared to 47% of patients treated with placebo. Oxymorphone hydrochloride extended-release tablets provided superior analgesia compared to placebo. The analgesic effect of oxymorphone hydrochloride extended-release tablets was maintained throughout the double-blind treatment period in 89% of patients who

completed the study. These patients reported a decrease, no change, or a ≤10 mm increase in VAS score from Day 7 until the end of the study.

The proportion of patients with various degrees of improvement from screening to study endpoint is shown in Figure 1. The figure is cumulative, so that patients whose change from baseline is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study were assigned 0% improvement.

Figure 1: Percent Reduction in Average Pain Intensity from Screening to Final Visit

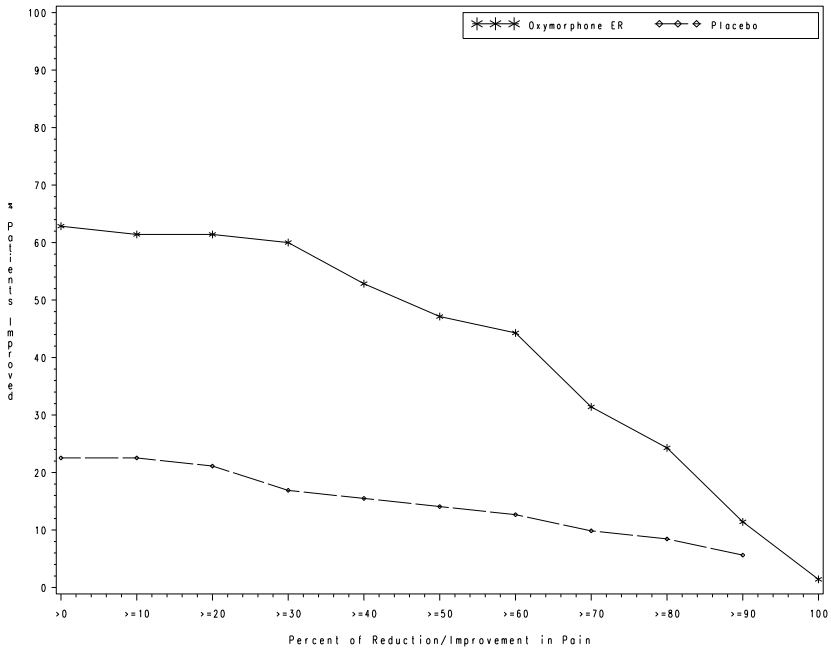


12-Week Study in Opioid-Experienced Patients with Low Back Pain

Patients on chronic opioid therapy entered a 4-week, open-label titration phase with oxymorphone hydrochloride extended-release tablets dosed every 12 hours at an approximated equianalgesic dose of their pre-study opioid medication. Of the patients who were able to stabilize within the Open-Label Titration Period, the mean±SD VAS score at Screening was 69.5±17.0 mm and at Baseline (beginning of Double-Blind Period) were 23.9±12.1 mm and 22.2±10.8 mm for the oxymorphone ER and placebo groups, respectively. Stabilized patients entered a 12-week double-blind treatment phase with placebo or their stabilized dose of oxymorphone hydrochloride extended-release tablets. The mean±SD stabilized doses were 80.9±59.3 mg and 93.3±61.3 mg for the oxymorphone hydrochloride extended-release tablets and placebo groups, respectively; total daily doses ranged from 20-260 mg. During the first 4 days of double-blind treatment, patients were allowed an unlimited number of OPANA 5 mg tablets, every 4-6 hours as supplemental analgesia; thereafter the number of OPANA was limited to two tablets per day. This served as a tapering method to minimize opioid withdrawal symptoms in placebo patients. Fifty seven percent of patients were titrated to a stabilized dose within approximately 4 weeks of oxymorphone hydrochloride extended-release tablets dose titration. Seventy percent of patients treated with oxymorphone hydrochloride extended-release tablets and 26% of patients treated with placebo completed the 12-week treatment. Oxymorphone hydrochloride extended-release tablets provided superior analgesia compared to placebo. The analgesic effect of oxymorphone hydrochloride extended-release tablets was maintained throughout the double-blind treatment period in 80 % of patients who completed the study. These patients reported a decrease, no change, or a ≤10 mm increase in VAS score from Day 7 until the end of the study.

The proportion of patients with various degrees of improvement from screening to study endpoint is shown in Figure 2. The figure is cumulative, so that patients whose change from baseline is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study were assigned 0% improvement.

Figure 2: Percent Reduction in Average Pain Intensity from Screening to Final Visit



16 HOW SUPPLIED/STORAGE AND HANDLING

OPANA ER extended-release tablets are supplied as follows:

5 mg

Pink, round, film-coated, biconcave extended-release tablets debossed with an “E” on one side and a “5” on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-812-60
Bottles of 100 with child-resistant closure	NDC 63481-812-70
Unit-Dose package of 20 tablets (2 blister cards of 10 tablets, not child-resistant, for hospital use only)	NDC 63481-812-20

7.5 mg

Gray, round, film coated, biconcave extended-release tablets debossed with an “E” on one side and a “7 ½” on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-813-60
Bottles of 100 with child-resistant closure	NDC 63481-813-70
Unit-Dose package of 20 tablets (2 blister cards of 10 tablets, not child-resistant, for hospital use only)	NDC 63481-813-20

10 mg

Light orange, round, film-coated, biconcave extended-release tablets debossed with an “E” on one side and a “10” on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-814-60
Bottles of 100 with child-resistant closure	NDC 63481-814-70
Unit-Dose package of 20 tablets (2 blister cards of 10 tablets, not child-resistant, for hospital use only)	NDC 63481-814-20

15 mg

White, round, film-coated, biconcave extended-release tablets debossed with an “E” on one side and a “15” on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-815-60
Bottles of 100 with child-resistant closure	NDC 63481-815-70
Unit-Dose package of 20 tablets (2 blister cards of 10 tablets, not child-resistant, for hospital use only)	NDC 63481-815-20

20 mg

Light green, round, film-coated, biconcave extended-release tablets debossed with an “E” on one side and a “20” on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-816-60
Bottles of 100 with child-resistant closure	NDC 63481-816-70
Unit-Dose package of 20 tablets (2 blister cards of 10 tablets, not child-resistant, for hospital use only)	NDC 63481-816-20

30 mg

Red, round, film-coated, biconcave extended-release tablets debossed with an “E” on one side and a “30” on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-817-60
Bottles of 100 with child-resistant closure	NDC 63481-817-70
Unit-Dose package of 20 tablets (2 blister cards of 10 tablets, not child-resistant, for hospital use only)	NDC 63481-817-20

40 mg

Light yellow to pale yellow, round, film-coated, biconcave extended-release tablets debossed with an “E” on one side and a “40” on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-818-60
Bottles of 100 with child-resistant closure	NDC 63481-818-70
Unit-Dose package of 20 tablets (2 blister cards of 10 tablets, not child-resistant, for hospital use only)	NDC 63481-818-20

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

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

17 PATIENT COUNSELING INFORMATION

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

Addiction, Abuse, and Misuse

Inform patients that the use of OPANA ER, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share OPANA ER with others and to take steps to protect OPANA ER 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 OPANA ER or when the dosage is increased, and that it can occur even at recommended doses *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

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

Interactions with Benzodiazepines and other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if OPANA ER is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

Instruct patients not to consume alcoholic beverages, as well as prescription and over-the-counter products that contain alcohol, during treatment with OPANA ER. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone *[see Warnings and Precautions (5.4)]*.

Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions

Inform patients that anaphylaxis and other hypersensitivity reactions have been reported with ingredients contained in OPANA ER. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Warnings and Precautions (5.6), Adverse Reactions (6)]*.

Serotonin Syndrome

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

MAOI Interaction

Inform patients to avoid taking OPANA ER while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking OPANA ER *[see Drug Interactions (7)]*.

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 (5.7)]*.

Important Administration Instructions

Instruct patients how to properly take OPANA ER, including the following:

- OPANA ER is designed to work properly only if swallowed intact. Taking cut, broken, chewed, crushed, or dissolved OPANA ER tablets can result in a fatal overdose *[see Dosage and Administration (2.1)]*.
- OPANA ER tablets should be taken one tablet at a time *[see Dosage and Administration (2.1)]*.
- Do not pre-soak, lick or otherwise wet the tablet prior to placing in the mouth *[see Dosage and Administration (2.1)]*.
- Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth *[see Dosage and Administration (2.1)]*.
- Occasionally, the inactive ingredients of OPANA ER may be eliminated as a soft mass in the stool that may resemble the original tablet. Inform patients that the active medication has already been absorbed by the time the patient sees the soft mass.
- Use OPANA ER exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression) *[see Dosage and Administration (2), Warnings and Precautions (2.1)]*.
- Do not discontinue OPANA ER without first discussing the need for a tapering regimen with the prescriber *[see Dosage and Administration (2.4), Warnings and Precautions (5.14)]*.

Hypotension

Inform patients that OPANA ER may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position).

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in OPANA ER. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of OPANA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that OPANA ER can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that breastfeeding is not recommended during treatment with OPANA ER *[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), Use in Specific Populations (8.3)]*.

Driving or Operating Heavy Machinery

Inform patients that OPANA ER 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), Clinical Pharmacology (12.2)]*.

Disposal of Unused OPANA ER

Advise patients to flush the unused tablets down the toilet when OPANA ER is no longer needed.

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Endo Pharmaceuticals Inc.
Malvern, PA 19355

Manufactured by:
Pharmaceuticals Manufacturing Research Services Inc.
Horsham, PA 19044

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117835

Medication Guide
OPANA®ER (Ō-pan-a) (oxymorphone hydrochloride) extended-release tablets, for oral use, CII

OPANA ER is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

Important information about OPANA ER:

- **Get emergency help right away if you take too much OPANA ER (overdose)**. When you first start taking OPANA ER, 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.
- Taking OPANA ER 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 your OPANA ER. They could die from taking it. Store OPANA ER away from children and in a safe place to prevent stealing or abuse. Selling or giving away OPANA ER is against the law.

Do not take OPANA ER if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking OPANA ER, tell your healthcare provider if you have a history of:

- head injury, seizures
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of OPANA ER during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended during treatment with OPANA ER. It may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking OPANA ER with certain other medicines can cause serious side effects that could lead to death.

When taking OPANA ER:

- Do not change your dose. Take OPANA ER exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 12 hours at the same time every day on an empty stomach, at least 1 hour before or 2 hours after meals. Do not take more than your prescribed dose in 24 hours. If you miss a dose, take your next dose at your usual time.
- Swallow OPANA ER whole. Do not cut, break, chew, crush, dissolve, snort, or inject OPANA ER because this may cause you to overdose and die.
- To avoid choking on the tablet OPANA ER should be taken 1 tablet at a time. Do not pre-soak, lick, or wet the tablet before placing in your mouth.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking OPANA ER without talking to your healthcare provider.**
- After you stop taking OPANA ER, flush any unused tablets down the toilet.

While taking OPANA ER DO NOT:

- Drive or operate heavy machinery, until you know how OPANA ER affects you. OPANA ER 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 OPANA ER may cause you to overdose and die.

The possible side effects of OPANA ER:

- 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 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 OPANA ER. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

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

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