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; and INTERACTION WITH ALCOHOL

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 each patient's risk before prescribing, and monitor regularly for development of these behaviors or 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 in 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)**

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

Boxed Warning	4/2014
Indications and Usage (1)	4/2014
Dosage and Administration (2)	4/2014
Warnings and Precautions (5)	4/2014

----------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----------

- For opioid-naïve and opioid non-tolerant patients, initiate with 5 mg tablets orally every 12 hours. (2.1)
- To convert to OPANA ER from another opioid, use available conversion factors to obtain estimated dose. (2.1)
- 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). (2.2)
- 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)
- Do not abruptly discontinue OPANA ER in a physically dependent patient. (2.3, 5.13)
- Instruct patients to swallow OPANA ER tablets intact. (2.4)
- Reduce the dose of OPANA ER in patients with mild hepatic impairment and patients with renal impairment. (2.5, 2.6)

----------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 (4)
- Known or suspected paralytic ileus and gastrointestinal obstruction (4)
- Hypersensitivity to oxymorphone (4)
- Moderate or severe hepatic impairment (4)

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

See Boxed WARNINGS

- Interaction with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, and death. If coadministration is required, consider dose reduction of one or both drugs because of additive pharmacological effects. (5.4)
- Elderly, cachectic, and debilitated patients and those with chronic pulmonary disease: Monitor closely because of increased risk for life-threatening respiratory depression. (5.5, 5.6)
- Hypotensive effect: Monitor during dose initiation and titration. (5.8)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression. Avoid use of OPANA ER in patients with impaired consciousness or coma susceptible to intracranial effects of CO_2 retention. (5.9)
- Use with caution in patients who have difficulty in swallowing or have underlying GI disorders that may predispose them to obstruction. (5.10)

----------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----------

- 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. (7.3)

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

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing mothers: Closely monitor infants of nursing women receiving OPANA ER. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 04/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and INTERACTION WITH ALCOHOL

***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; and INTERACTION WITH ALCOHOL

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 or 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)]*.

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, 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 Initial Dosing

To avoid medication errors, prescribers and pharmacists must be aware that oxymorphone is available as both immediate-release 5 mg and 10 mg tablets and extended-release 5 mg and 10 mg tablets *[see Dosage Forms and Strengths (3)]*.

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

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with OPANA ER *[see Warnings and Precautions (5.2)]*.

OPANA ER tablets must be taken 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)]*.

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 who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 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 (active opioid) daily dose.
- For patients on a regimen of more than one opioid, calculate the approximate oral (active opioid) dose for each opioid and sum the totals to obtain the approximate total (active opioid) 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 (active opioid) 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 (active opioid) 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.

2.2 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.

2.3 Discontinuation of OPANA ER
When a patient no longer requires therapy with OPANA ER, use a gradual downward titration of the dose every two to four days, to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue OPANA ER.

2.4 Administration of OPANA ER
Instruct patients to swallow OPANA ER tablets intact. The tablets are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of oxymorphone *[see Warnings and Precautions (5.2)]*. Administer on an empty stomach, at least 1 hour prior to or 2 hours after eating.

2.5 Patients with 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 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 Geriatric Patients
The steady-state plasma concentrations of oxymorphone are approximately 40% 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

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