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, CII

Initial U.S. Approval: 1959

WARNING: POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE

See full prescribing information for complete boxed warning.

- **OPANA ER contains oxymorphone which is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid analgesics. (9)**
- **Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OPANA ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9)**
- **OPANA ER is NOT intended for use as an as needed analgesic. (1)**
- **OPANA ER tablets are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed as this leads to rapid release and absorption of a potentially fatal dose of oxymorphone. (2)**
- **Patients must not consume alcoholic beverages, prescription or non-prescription medications containing alcohol. Co-ingestion of alcohol with OPANA ER may result in a potentially fatal overdose of oxymorphone. (2)**

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

- OPANA ER is an opioid agonist indicated for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time. (1)
- Not intended for use as an as needed analgesic. Not indicated in the immediate post-operative period or if the pain is mild or not expected to persist for an extended period of time. (1)

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

- Administered on an empty stomach, at least 1 hour prior to or 2 hours after eating. (2.2)
- Symmetrical, every 12h dosing is appropriate for the majority of patients. (2.1)
- Opioid-Naïve Patients: Initiate treatment with 5 mg every 12 hours. (2.2)
- Opioid-Experienced Patients: Ratios as a guide to convert only from other opioids to OPANA ER. (2.2)
- Individualize treatment; titrate to effective and tolerable dose. (2.1)
- Don't stop abruptly (9.3); taper gradually to stop treatment (2.8)

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

- Extended-Release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg

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

- Known hypersensitivity to oxymorphone, any other ingredients in OPANA ER, or morphine analogs. (4)
- Respiratory depression (4)
- Acute or severe bronchial asthma or hypercarbia (4)
- Paralytic ileus (4)
- Moderate or severe hepatic impairment (4)

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

See Boxed WARNINGS

- Respiratory depression: Increased risk in elderly, debilitated patients, and those suffering from conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve. (5.2)
- Misuse, abuse, and diversion: OPANA ER is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. (5.3)
- CNS effects: Additive CNS-depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. (5.4)
- Head Injury: Effects may be markedly exaggerated. Administer with extreme caution. (5.5)
- Hypotensive effect: Increased risk with compromised ability to maintain blood pressure. Administer with caution to patients in circulatory shock. (5.6)
- Mild hepatic impairment: Use with caution and at lower doses due to higher plasma concentrations than in patients with normal hepatic function. (5.7)
- Prolonged gastric obstruction: May occur in patients with gastrointestinal obstruction. (5.9)
- Sphincter of Oddi: Administer with caution in patients with biliary tract disease. (5.11)
- Impaired mental/physical abilities: Caution must be used with potentially hazardous activities (5.12)

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

- CNS depressants: Increased risk of respiratory depression, hypotension, profound sedation, coma or death. When combined therapy with CNS depressant is contemplated, the dose of one or both agents should be reduced. (7.2)
- Mixed agonist/antagonist opioids (i.e., pentazocine, nalbuphine, and butorphanol): May reduce analgesic effect and/or precipitate withdrawal symptoms. (7.3)
- Cimetidine: Combination use may precipitate confusion, disorientation, respiratory depression, apnea, seizures. (7.4)
- Anticholinergics: May result in urinary retention and/or severe constipation, which may lead to paralytic ileus. (7.5)
- Monoamine oxidase inhibitors (MAOIs): Potentiate the action of opioids. OPANA ER should not be used in patients taking MAOIs or within 14 days of stopping such treatment. (7.6)
- Dose adjustment for CYP3A450 or 2C9-mediated drug-drug interactions is not required. (7.1)

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

- Pregnancy: Not recommended during labor and delivery, pregnancy, or nursing. (8.1)
- Geriatric Patients – OPANA ER should be used with caution in elderly patients. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA – approved patient labeling

Revised: 09/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE

Potential for Abuse

OPANA ER contains oxymorphone, which is a morphine-like opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. (9)

Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OPANA ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9.2)

Proper Patient Selection

OPANA ER is an extended-release oral formulation of oxymorphone indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)

Limitations of Use

OPANA ER is NOT intended for use as an as needed analgesic. (1)

OPANA ER TABLETS are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed OPANA ER TABLETS leads to rapid release and absorption of a potentially fatal dose of oxymorphone. (2)

Patients must not consume alcoholic beverages, or prescription or non-prescription medications 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. (2)

1 INDICATIONS AND USAGE

OPANA ER is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

Limitations of Usage

OPANA ER is not intended for use as an as needed analgesic.

OPANA ER is not indicated for pain in the immediate post-operative period if the pain is mild, or not expected to persist for an extended period of time.

OPANA ER is only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate or severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines).

2 DOSAGE AND ADMINISTRATION

2.1 Safe Administration Instructions

OPANA ER tablets are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed OPANA ER TABLETS leads to rapid release and absorption of a potentially fatal dose of oxymorphone.

Patients must not consume alcoholic beverages, or prescription or non-prescription medications 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.

While symmetric (same dose AM and PM), around-the-clock, every 12 hours dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one extended-release opioid for around-the-clock therapy.

Selection of patients for treatment with OPANA ER should be governed by the same principles that apply to the use of other extended-release opioid analgesics *[see Indications and Usage (1)]*. Physicians should individualize treatment in every case, using non-opioid analgesics, opioids on an as needed basis, combination products, and chronic opioid therapy in a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Healthcare

professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring *[see Boxed Warning]*.

2.2 Initiating Therapy with OPANA ER

It is necessary to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of OPANA ER, attention should be given to the following:

- total daily dose, potency and specific characteristics of the opioid the patient has been taking previously;
- relative potency estimate used to calculate the equivalent oxymorphone dose needed;
- patient's degree of opioid tolerance;
- age, general condition, and medical status of the patient;
- concurrent non-opioid analgesics and other medications;
- type and severity of the patient's pain;
- balance between pain control and adverse experiences;
- risk factors for abuse or addiction, including a prior history of abuse or addiction.

Once therapy is initiated, frequently assess pain relief and other opioid effects. Base the titration of the total daily OPANA ER dose upon the amount of supplemental opioid utilization, severity of the patient's pain, and the patient's ability to tolerate the opioid. Titrate dose to generally mild or no pain with the regular use of no more than two doses of supplemental analgesia, i.e. "rescue," per 24 hours. Patients who experience breakthrough pain may require dosage adjustment.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of an immediate-release opioid, or a non-opioid analgesic may be administered. Adjust dosing to obtain an appropriate balance between pain relief and opioid-related adverse experiences. If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are adequately managed, continue upward titration to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient and the caregiver/family. Advise patients and caregivers/family members of the potential adverse reactions.

The dosing recommendations below, therefore, can only be considered as suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of each individual patient.

Titrate dose to adequate pain relief (generally mild or no pain).

Administer OPANA ER on an empty stomach, at least one hour prior to or two hours after eating *[see Clinical Pharmacology (12.3)]*.

Opioid-Naïve Patients

The initial dose for patients who are not opioid-experienced and who are being initiated on chronic around-the-clock opioid therapy with OPANA ER is 5 mg every 12 hours. Thereafter, titrate the dose individually at increments of 5-10 mg every 12 hours every 3-7 days, to a level that provides adequate analgesia and minimizes side effects under the close supervision of the prescribing physician.

Opioid-Experienced Patients

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

Given OPANA ER's absolute oral bioavailability of approximately 10%, patients receiving parenteral oxymorphone may be converted 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

For conversion from other opioids to OPANA ER, physicians and other healthcare professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate. In general, it is safest to start the OPANA ER therapy by administering half of the calculated total daily dose of OPANA ER (see conversion ratio table below) in 2 divided doses, every 12 hours. Gradually adjust the initial dose of OPANA ER until adequate pain relief and acceptable side effects have been achieved.

The following table provides approximate equivalent doses, which may be used as a guideline for conversion. **The conversion ratios and approximate equivalent doses in this conversion table are only to be used for the conversion from current opioid therapy to OPANA ER.** In a Phase 3 clinical trial with an open-label titration period, patients were converted from their current opioid to OPANA ER using the following table as a guide. There is substantial patient variation in the relative potency of different opioid drugs and formulations.

CONVERSION RATIOS TO OPANA ER

Opioid	Approximate Equivalent Dose Oral	Oral Conversion Ratio[a]
Oxymorphone	10 mg	1
Hydrocodone	20 mg	0.5
Oxycodone	20 mg	0.5
Methadone[b]	20 mg	0.5
Morphine	30 mg	0.333

[a] Ratio for conversion of oral opioid dose to approximate oxymorphone equivalent dose. Select opioid and multiply the dose by the conversion ratio to calculate the approximate oral oxymorphone equivalent.

- **The conversion ratios and approximate equivalent doses in this conversion table are only to be used for the conversion from current opioid therapy to OPANA ER.**
- Sum the total daily dose for the opioid and multiply by the conversion ratio to calculate the oxymorphone total daily dose.
- For patients on a regimen of mixed opioids, calculate the approximate oral oxymorphone dose for each opioid and sum the totals to estimate the total daily oxymorphone dose.
- The dose of OPANA ER can be gradually adjusted, preferably at increments of 10 mg every 12 hours every 3-7 days, until adequate pain relief and acceptable side effects have been achieved [*see Dosage and Administration (2.1)*].

[b] **It is extremely important to monitor all patients closely 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 tends to accumulate in the plasma.

No dose adjustment for CYP 3A4- or 2C9-mediated drug-drug interactions is required *[see Clinical Pharmacology (12.3)]*.

2.3 Patients with Hepatic Impairment

Start patients with mild hepatic impairment with the lowest dose and titrate slowly while carefully monitoring side effects. OPANA ER is contraindicated in patients with moderate or severe hepatic impairment *[see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)]*.

2.4 Patients with Renal Impairment

There are 57% and 65% increases in oxymorphone bioavailability in patients with moderate and severe renal impairment, respectively *[see Clinical Pharmacology (12.3)]*. Accordingly, in patients with creatinine clearance rates less than 50 mL/min, start OPANA ER with the lowest dose and titrate slowly while carefully monitoring side effects.

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