OPANA ER - oxymorphone hydrochloride tablet
Bryant Ranch Prepack

HIGHLIGHTS OF PRESCRIBING INFORMATION
Opana ER 20 mg 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

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- 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

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

DOSAGE FORMS AND STRENGTHS

- Extended-Release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg (3)

CONTRAINDICATIONS

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

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

Adverse reactions in greater than or equal to 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

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

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

See 17 for FDA-approved patient labeling.

Revised: 12/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

Enter section text here

Enter section text here

Enter section text here

Enter section text here

Enter section text here

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BOXED WARNING

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

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 2.2 Initiating Therapy with OPANA ER 2.3 Patients with Hepatic Impairment 2.4 Patients with Renal Impairment 2.5 Use with Central Nervous System Depressants 2.6 Geriatric Patients 2.7 Maintenance of Therapy 2.8 Cessation of Therapy

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	
	Approximate Equivalent Dose	Oral
Opioid	Oral	Conversion Ratioa
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
aRatio 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.

2.5 Use with Central Nervous System Depressants In patients who are concurrently receiving other central nervous system (CNS) depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol, start OPANA ER at 1/3 to 1/2 of the usual dose because respiratory depression, hypotension, and profound sedation, coma or death may result [see Warnings and Precautions (5.4) and Drug Interactions (7.2)].

Although no specific interaction between oxymorphone and monoamine oxidase inhibitors has been observed, OPANA ER is not recommended for use in patients who have received MAO inhibitors within 14 days [see Drug Interactions (7.6)].

2.6 Geriatrics Patients
The steady-state plasma concentrations of oxymorphone are approximately 40% higher in elderly subjects than in young subjects. Exercise caution in the selection of the starting dose of OPANA ER for an elderly patient by starting at the low end of the dosing range and slowly titrating to adequate analgesia [see Clinical Pharmacology (12.3) and Use in Specific Populations (8.5)].

2.7 Maintenance of Therapy
During chronic therapy with OPANA ER, periodically reassess the continued need for around-the-clock opioid therapy. Continue to assess patients for their clinical risks for opioid abuse, addiction, or

diversion particularly with high-dose formulations. If patients need to titrate while on maintenance therapy, follow the same method outlined in Initiating Therapy with OPANA ER.

2.8 Cessation of Therapy
When the patient no longer requires therapy with OPANA ER tablets, gradually taper doses to prevent signs and symptoms of withdrawal in the physically dependent patient.

3 DOSAGE FORMS AND STRENGTHS

3 DOSAGE FORMS AND STRENGTHS

The 5 mg dosage form is a pink, octagon shape, film coated, convex extended-release tablets debossed with “5” on one side and plain on the other.

The 7.5 mg dosage form is a gray, octagon shape, film coated, convex extended-release tablets debossed with “7 ½” on one side and plain on the other.

The 10 mg dosage form is a light orange, octagon shape, film coated, convex extended-release tablets debossed with “10” on one side and plain on the other.

The 15 mg dosage form is a white, octagon shape, film coated, convex extended-release tablets debossed with “15” on one side and plain on the other.

The 20 mg dosage form is a light green, octagon shape, film coated, convex extended-release tablets debossed with “20” on one side and plain on the other.

The 30 mg dosage form is a red, octagon shape, film coated, convex extended-release tablets debossed with “30” on one side and plain on the other.

The 40 mg dosage form is a yellow, octagon shape, film coated, convex extended-release tablets debossed with “40” on one side and plain on the other.

4 CONTRAINDICATIONS

4 CONTRAINDICATIONS

OPANA ER is contraindicated in patients who have:

- significant respiratory depression
- or are suspected of having paralytic ileus
- acute or severe bronchial asthma or hypercarbia
- moderate and severe hepatic impairment [see Clinical Pharmacology (12.3), Warnings and Precautions (5.7),].
- known hypersensitivity to any of its components or the active ingredient, oxymorphone or with known hypersensitivity to morphine analogs such as codeine.

5 WARNINGS AND PRECAUTIONS 5.1 Information Essential for Safe Administration 5.2 Respiratory Depression 5.3 Misuse, Abuse and Diversion of Opioids 5.4 Interactions with Alcohol and other CNS Depressants 5.5 Use in Patients with Head Injury and Increased Intracranial Pressure 5.6 Hypotensive Effect 5.7 Hepatic Impairment 5.8 Special Risk Groups 5.9 Gastrointestinal Effects 5.10 Ambulatory Surgery and Post Operative Use 5.11 Use in Pancreatic/Biliary Tract Disease 5.12 Driving and Operating Machinery

5 WARNINGS AND PRECAUTIONS

5.1 Information Essential for Safe Administration

OPANA ER tablets are to be swallowed whole, and are not to be broken, chewed, crushed or dissolved. Taking broken, chewed, crushed or dissolved OPANA ER tablets could lead to the rapid release and absorption of a potentially fatal dose of oxymorphone [see Boxed Warning].

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 [see Pharmacokinetics (12.3)].

Instruct patients against use by individuals other than the patient for whom OPANA ER was prescribed, as such inappropriate use may have severe medical consequences, including death.

5.2 Respiratory Depression

Respiratory depression is the chief hazard of OPANA ER. Respiratory depression is a potential problem in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Administer OPANA ER with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma. In these patients, even usual therapeutic doses of oxymorphone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Consider alternative non-opioid analgesics and use OPANA ER only under careful medical supervision at the lowest effective dose in such patients.

5.3 Misuse, Abuse and Diversion of Opioids

OPANA ER contains oxymorphone, a mu opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

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

OPANA ER tablets may be abused by crushing, chewing, snorting or injecting the product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death [see Drug Abuse and Dependence (9)].

OPANA ER may be targeted for theft and diversion. Healthcare professionals should contact their State Medical Board, State Board of Pharmacy, or State Control Board for information on how to detect or prevent diversion of this product, and security requirements for storing and handling of OPANA ER.

Healthcare professionals should advise patients to store OPANA ER in a secure place, preferably locked and out of the reach of children and other non-caregivers.

Concerns about abuse, misuse, diversion and addiction should not prevent the proper management of pain.

5.4 Interactions with Alcohol and other CNS Depressants
Patients receiving other opioid analgesics, general anesthetics, phenothiazines or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with oxymorphone may experience respiratory depression, hypotension, profound sedation, coma and death [see Drug Interactions (7.2)]. Avoid concurrent use of alcohol and OPANA ER [see Pharmacokinetics (12.3)].

5.5 Use in Patients with Head Injury and Increased Intracranial Pressure
In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of opioid analgesics and their potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on papillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Administer OPANA ER with extreme caution to patients who may be particularly susceptible to the intracranial effects of CO_2 retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

5.6 Hypotensive Effect
OPANA ER may cause severe hypotension in a patient whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents that compromise vasomotor tone. Administer OPANA ER with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

5.7 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)]. Use OPANA ER with caution in patients with mild impairment, starting with the lowest dose and titrating slowly while carefully monitoring for side effects [see Dosage and Administration (2.3)]. OPANA ER is contraindicated in patients with moderate or severe hepatic impairment.

5.8 Special Risk Groups
Use OPANA ER with caution in the following conditions: adrenocortical insufficiency (e.g., Addison's disease), prostatic hypertrophy or urethral stricture, severe impairment of pulmonary or renal function, and toxic psychosis.

Opioids may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings.

5.9 Gastrointestinal Effects
OPANA ER decreases bowel motility. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract. Monitor for decreased bowel motility in post-operative patients receiving opioids. The administration of OPANA ER may obscure the diagnosis or clinical course in patients with acute abdominal conditions. OPANA ER is contraindicated in patients with paralytic ileus.

5.10 Ambulatory Surgery and Post-Operative Use
OPANA ER is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

OPANA ER is only indicated for postoperative use in the patient if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to 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).

Patients who are already receiving OPANA ER as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention.

5.11 Use in Pancreatic/Biliary Tract Disease
OPANA ER, like other opioids, may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

5.12 Driving and Operating Machinery
Opioid analgesics impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.

6 ADVERSE REACTIONS 6.1 Clinical Trial Experience

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Respiratory depression [see Warnings and Precautions (5.2)]
- Misuse and abuse [see Warning and Precautions (5.3) and Drug Abuse and Dependence (9)]
- CNS depressant effects [see Warnings and Precautions (5.4)]

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 OPANA ER was evaluated in a total of 2011 patients in controlled clinical trials. The clinical trials consisted of patients with moderate to severe chronic non-malignant pain, cancer pain, and post surgical pain.

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 Events Reported in greater than or equal to 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	
	OPANA ER	OPANA ER	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 Events Reported in greater than or equal to 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	
	OPANA ER	OPANA ER	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 greater than or equal to 2% in Patients Receiving OPANA ER.

MedDRA Preferred Term	OPANA ER (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%	less than 1%
Sedation	6%	8%
Diarrhea	4%	6%
Insomnia	4%	2%
Fatigue	4%	1%
Appetite decreased	3%	less than 1%
Abdominal pain	3%	2%

The common (greater than or equal to 1% to less than 10%) adverse drug reactions reported at least once by patients treated with OPANA ER 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 less than 1% in the OPANA ER trials include the following: Bradycardia, palpitation, syncope, tachycardia, postural hypotension, miosis, visual disturbance, abdominal distention, ileus, feeling jittery, hot flashes, allergic reactions, hypersensitivity, urticaria, oxygen saturation decreased, central nervous system depression, depressed level of consciousness, agitation, dysphoria, euphoric mood, hallucination, mental impairment, mental status changes, difficult micturition, urinary retention, hypoxia, respiratory depression, respiratory distress, respiratory rate decreased, clamminess, dermatitis, hypotension.

7 DRUG INTERACTIONS 7.1 Drug-Drug Interactions 7.2 Use in CNS Depressants 7.3 Interactions with Mixed Agonist/Antagonist Opioid Analgesics 7.4 Cimetidine 7.5 Anticholinergics 7.6 MAO Inhibitors

7 DRUG INTERACTIONS

7.1 Drug-Drug Interactions
Oxymorphone is highly metabolized principally in the liver and undergoes reduction or conjugation with glucuronic acid to form both active and inactive metabolites [see Pharmacokinetics (12.3)]). Clinical drug interaction studies with OPANA ER showed no induction of CYP450 3A4 or 2C9 enzyme activity, indicating that no dose adjustment for CYP 3A4- or 2C9-mediated drug-drug interactions is required [see Clinical Pharmacology (12.3)].

7.2 Use with CNS Depressants
The concomitant use of other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol may produce additive CNS depressant effects. OPANA ER should be started at 1/3 to 1/2 of the usual dose in patients who are concurrently receiving other central nervous system depressants because respiratory depression, hypotension, and profound sedation, coma and death may result, and titrated slowly as necessary for adequate pain relief.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced [see Dosage and Administration (2.5) and Warnings and Precautions (5.4)].

7.3 Interactions with Mixed Agonist/Antagonist Opioid Analgesics
Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, or buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic, such as oxymorphone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxymorphone and/or may precipitate withdrawal symptoms.

7.4 Cimetidine
CNS side effects have been reported (e.g., confusion, disorientation, respiratory depression, apnea, seizures) following coadministration of cimetidine with opioid analgesics; a causal relationship has not been established.

7.5 Anticholinergics
Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid

analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

7.6 MAO Inhibitors
OPANA ER is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. No specific interaction between oxymorphone and MAO inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on fetal development. The use of OPANA ER in pregnancy, in nursing mothers, or in women of child-bearing potential requires that the possible benefits of the drug be weighed against the possible hazards to the mother and the child.

Prolonged use of opioid analgesics during pregnancy may cause fetal-neonatal physical dependence.

Teratogenic Effects
Pregnancy Category C
There are no adequate and well-controlled studies of oxymorphone in pregnant women. OPANA ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [see Use in Specific Populations (8.2)].

Oxymorphone hydrochloride administration did not cause malformations at any doses evaluated during developmental toxicity studies in rats (less than or equal to 25 mg/kg/day) or rabbits (less than or equal to 50 mg/kg/day). These doses are 3-fold and 12-fold the human dose of 40 mg every 12 hours, based on body surface area. There were no developmental effects in rats treated with 5 mg/kg/day or rabbits treated with 25 mg/kg/day. Fetal weights were reduced in rats and rabbits given doses of greater than or equal to 10 mg/kg/day and 50 mg/kg/day, respectively. These doses are 1.2-fold and 12-fold the human dose of 40 mg every 12 hours based on body surface area, respectively. There were no effects of oxymorphone hydrochloride on intrauterine survival in rats at doses less than or equal to 25 mg/kg/day, or rabbits at less than or equal to 50 mg/kg/day in these studies (see Non-teratogenic Effects, below). In a study that was conducted prior to the establishment of Good Laboratory Practices (GLP) and not according to current recommended methodology, a single subcutaneous injection of oxymorphone hydrochloride on gestation day 8 was reported to produce malformations in offspring of hamsters that received 15.5-fold the human dose of 40 mg every 12 hours based on body surface area. This dose also produced 20% maternal lethality.

Non-teratogenic Effects
Oxymorphone hydrochloride administration to female rats during gestation in a pre- and postnatal developmental toxicity study reduced mean litter size (18%) at a dose of 25 mg/kg/day, attributed to an increased incidence of stillborn pups. An increase in neonatal death occurred at greater than or equal to 5 mg/kg/day. Post-natal survival of the pups was reduced throughout weaning following treatment of the dams with 25 mg/kg/day. Low pup birth weight and decreased postnatal weight gain occurred in pups born to oxymorphone-treated pregnant rats given a dose of 25 mg/kg/day. This dose is ~ 3-fold higher than the human dose of 40 mg every 12 hours on a body surface area basis.

8.2 Labor and Delivery

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression in neonates. 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. Occasionally, opioid analgesics may 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.

Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, such as naloxone or nalmefene, should be available for reversal of opioid-induced respiratory depression in the neonate.

Upon delivery from a mother who received opioids for a long period of time, neonatal withdrawal may occur. Symptoms usually appear during the first days of life and may include convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhea, sneezing, yawning, and increased respiratory rate.

8.3 Nursing Mothers

8.3 Nursing Mothers

It is not known whether oxymorphone is excreted in human milk. Because many drugs, including some opioids, are excreted in human milk, caution should be exercised when OPANA ER is administered to a nursing woman. Infants exposed to OPANA ER through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.4 Pediatric Use

8.4 Pediatric Use

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

8.5 Geriatric Use 8.6 Hepatic Impairment 8.7 Renal Impairment

8.5 Geriatric Use
OPANA ER should be used with caution in elderly patients [see Clinical Pharmacology 12.3)].

Of the total number of subjects in clinical studies of OPANA ER, 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.

8.6 Hepatic Impairment
In a PK study of OPANA ER, patients with mild hepatic impairment were shown to have an increase in bioavailability of 1.6 fold. Use OPANA ER with caution in patients with mild impairment. Start these patients on the lowest dose and titrate slowly while carefully monitoring for side effects. OPANA ER is contraindicated for patients with moderate and severe hepatic impairment [see Contraindications (4), Warnings and Precautions (5.7), and Dosage and Administration (2.3)].

8.7 Renal Impairment
In a PK study of OPANA ER, patients with moderate to severe renal impairment were shown to have an increase in bioavailability ranging from 57-65% [see Clinical Pharmacology (12.3)]. Start these patients with the lowest dose of OPANA ER and titrate slowly while monitored for side effects [see Dosage and Administration (2.4)].

9 DRUG ABUSE AND DEPENDENCE 9.1 Controlled Substance

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OPANA ER contains oxymorphone, a mu opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine and other opioids. Oxymorphone can be abused and is subject to criminal diversion [see Warning and Precautions (5.3)].

9.2 Abuse

9.2 Abuse

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. Addiction is characterized by one or more of the following: impaired control over drug use, compulsive use, use for non-medical purposes, and continued use despite harm. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

"Drug seeking" behavior is very common to addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(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. Physicians 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 and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OPANA ER, like other opioids, may be diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

OPANA ER is intended 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. Parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV.

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.

9.3 Dependence

9.3 Dependence

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

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). The development of physical dependence and tolerance is not unusual during chronic opioid therapy.

OPANA ER should not be abruptly discontinued [see Dosage and Administration (2.8)]. If OPANA ER is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other 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 symptoms [see Use in Specific Populations (8.1, 8.2)].

10 OVERDOSAGE 10.1 Symptoms 10.2 Treatment

10 OVERDOSAGE

10.1 Symptoms

Acute overdosage with OPANA ER is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils and sometimes bradycardia and hypotension. In some cases, apnea, circulatory collapse, cardiac arrest and death may occur.

OPANA ER may cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [see Clinical Pharmacology (12.2)].

10.2 Treatment

In the treatment of OPANA ER overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression that may result from overdosage or unusual sensitivity to opioids including OPANA ER. Nalmefene is an alternative pure opioid antagonist, which may be administered as a specific antidote to respiratory

depression resulting from opioid overdose. Since the duration of action of OPANA ER may exceed that of the antagonist, keep the patient under continued surveillance and administer repeated doses of the antagonist according to the antagonist labeling as needed to maintain adequate respiration.

In patients receiving OPANA ER, opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression. Administer opioid antagonists cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including OPANA ER. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If respiratory depression is associated with muscular rigidity, administration of a neuromuscular blocking agent may be necessary to facilitate assisted or controlled ventilation. Muscular rigidity may also respond to opioid antagonist therapy.

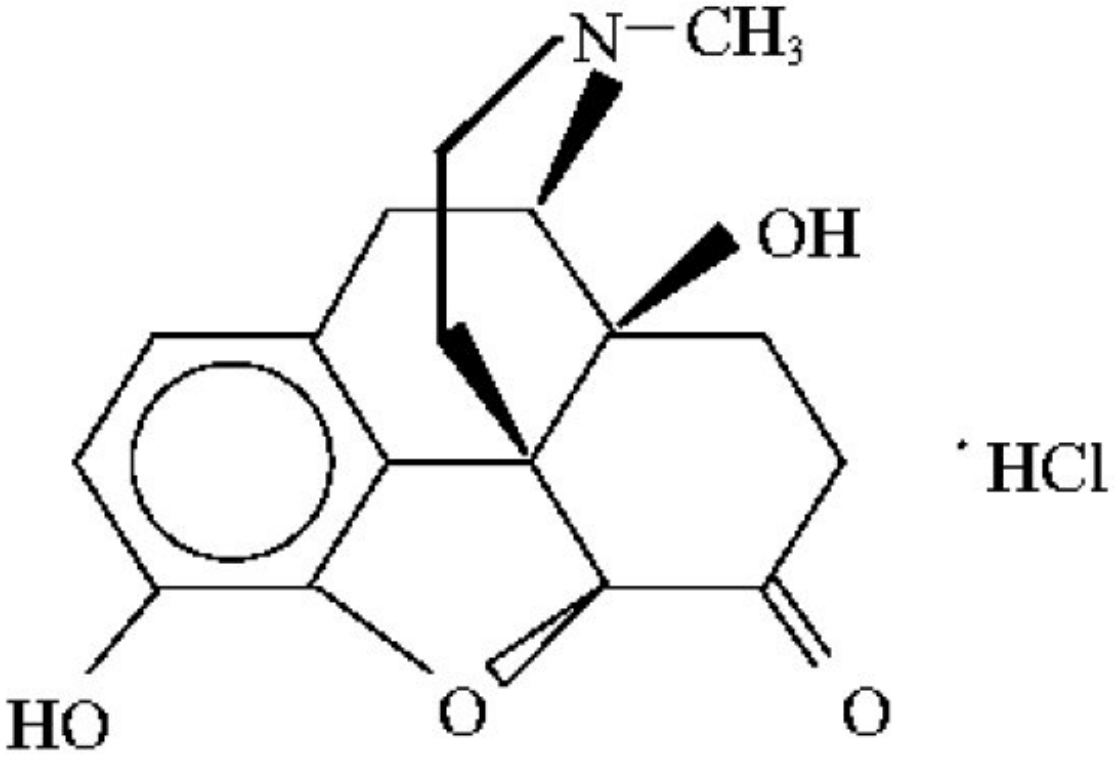
11 DESCRIPTION

11 DESCRIPTION

OPANA ER (oxymorphone hydrochloride) extended-release is a semi-synthetic opioid analgesic 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, methylparaben, silicified microcrystalline cellulose, sodium stearyl fumarate, TIMERx□□-N, titanium dioxide, and triacetin. The 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg tablets also contain macrogol, and polysorbate 80. 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 FDandC yellow No. 6. The 20 mg tablets contain FDandC blue No. 1, FDandC yellow No. 6, and DandC yellow No. 10. The 40 mg tablets contain FDandC yellow No. 6, DandC yellow No. 10, and lactose monohydrate.

Chemically, oxymorphone hydrochloride is 4, 5□-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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxymorphone, a pure opioid agonist, is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses.

The precise mechanism of analgesia, the principal therapeutic action of oxymorphone, is unknown. Specific central nervous system (CNS) opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression and perception of analgesic effects. In addition, opioid receptors have also been identified within the peripheral nervous system (PNS). The role that these receptors play in these drugs' analgesic effects is unknown.

12.2 Pharmacodynamics

12.2 Pharmacodynamics

Concentration-Efficacy Relationships
The minimum effective plasma concentration of oxymorphone for analgesia varies widely among patients, especially among patients who have been previously treated with agonist opioids. As a result, individually titrate patients to achieve a balance between therapeutic and adverse effects. The minimum effective analgesic concentration of oxymorphone for any individual patient may increase over time due

to an increase in pain, progression of disease, development of a new pain syndrome and/or potential development of analgesic tolerance.

Concentration-Adverse Experience Relationships
There is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression.

As with all opioids, the dose of OPANA ER must be individualized [see Dosage and Administration (2.1)]. The effective analgesic dose for some patients will be too high to be tolerated by other patients.

Effects on the Central Nervous System (CNS)
The principal therapeutic action of oxymorphone is analgesia. In common with other opioids, oxymorphone causes respiratory depression, in part by a direct effect on the brainstem 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. Opioids depress the cough reflex by direct effect on the cough center in the medulla.

Oxymorphone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [see Overdosage (10.1)]. Other therapeutic effects of oxymorphone include anxiolysis, euphoria and feeling of relaxation.

In addition to analgesia, the widely diverse effects of oxymorphone include drowsiness, changes in mood, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous system [see Clinical Pharmacology (12.1)].

Effects on the Gastrointestinal Tract and on Other Smooth Muscle
Gastric, biliary and pancreatic secretions are decreased by oxymorphone. 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. The end result may be constipation. Oxymorphone can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi, and transient elevations in serum amylase. Oxymorphone may also cause spasm of the sphincter of the urinary bladder.

Cardiovascular System Effects
Opioids produce peripheral vasodilation which may result in orthostatic hypotension. Release of histamine can occur and may contribute to opioid-induced hypotension. Manifestations of histamine release may include orthostatic hypotension, pruritus, flushing, red eyes, and sweating. Animal studies have shown that oxymorphone has a lower propensity to cause histamine release than other opioids.

Endocrine System Effects
Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Immune System Effects
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.

12.3 Pharmacokinetics

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 OPANA ER, for both peak plasma levels (Cmax) and extent of absorption (AUC) (see Table 4).

Table 4: Mean (±SD) OPANA ER Pharmacokinetic Parameters

Regimen	Dosage	Cmax (ng/mL)	AUC (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 Dosea	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 OPANA ER in healthy volunteers. In both studies, after the administration of OPANA ER, the Cmax was increased by approximately 50% in fed subjects compared to fasted subjects. A similar increase in Cmax 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 OPANA ER. 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 (2.2)].

Ethanol Effect
In Vivo OPANA ER Formulation-Alcohol Interaction
Although in vitro studies have demonstrated that OPANA ER does not release oxymorphone more rapidly in 500 mL of 0.1N HCl solutions containing ethanol (4%, 20%, and 40%), there is an in vivo interaction with alcohol. An in vivo study examined the effect of alcohol (40%, 20%, 4% and 0%) on the bioavailability of a single dose of 40 mg of OPANA ER in healthy, fasted volunteers. The results showed that the oxymorphone mean AUC was 13% higher (not statistically significant) after co-administration of 240 mL of 40% alcohol. The AUC was essentially unaffected in subjects following the co-administration of OPANA ER and ethanol (240 mL of 20% or 4% ethanol).

There was a highly variable effect on Cmax with concomitant administration of alcohol and OPANA ER. The change in Cmax ranged from a decrease of 50% to an increase of 270% across all conditions studied. Following concomitant administration of 240 mL of 40% ethanol the Cmax increased on average by 70% and up to 270% in individual subjects. Following the concomitant administration of 240 mL of 20% ethanol, the Cmax increased on average by 31% and up to 260% in individual subjects. Following the concomitant administration of 240 mL of 4 % ethanol, the Cmax 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 Tmax is 2 hours. Following co-administration of OPANA ER and alcohol (240 mL of 40% ethanol) in fasted subjects, the mean peak oxymorphone level is 3.9 ng/mL and the median Tmax is 1.5 hours (range 0.75 – 6 hours).

Co-administration of oxymorphone and ethanol must be avoided.

Oxymorphone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation, coma, or death may result.

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%.

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-oymorphone 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, less than 1% of the administered dose is excreted unchanged in the urine. On average, 33% to 38% of the administered dose is excreted in the urine as oxymorphone-3-glucuronide and 0.25% to 0.62% 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.

Pharmacokinetics in Special Populations
Elderly
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 Cmax. This observation does not appear related to a difference in body weight, metabolism, or excretion of oxymorphone [see Use in Specific Populations (8.5)].

Gender
The effect of gender was evaluated following single- and multiple-doses of OPANA ER in male and female adult volunteers. There was a consistent tendency for female subjects to have slightly higher AUCss and Cmax values than male subjects; however, gender differences were not observed when

AUCss and Cmax were adjusted by body weight.

Hepatic Impairment
The liver plays an important role in the pre-systemic clearance of orally administered oxymorphone. Accordingly, the bioavailability of orally administered oxymorphone may be markedly increased in patients with moderate to severe liver disease. The disposition of oxymorphone was compared in 6 patients with mild, 5 patients with moderate, and one patient with severe hepatic impairment and 12 subjects with normal hepatic function. The bioavailability of oxymorphone was increased by 1.6-fold in patients with mild hepatic impairment and by 3.7-fold in patients with moderate hepatic impairment. In one patient with severe hepatic impairment, the bioavailability was increased by 12.2-fold. The half-life of oxymorphone was not significantly affected by hepatic impairment.

Renal Impairment
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 less than 30 mL/min; n=8) patients, respectively, compared to healthy controls.

Drug-Drug Interactions
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 less than or equal to 50 µM. An inhibition of CYP3A4 activity occurred at oxymorphone concentrations greater than or equal to 150 µM. Therefore, it is not expected that oxymorphone, or its metabolites will act as inhibitors of any of the major CYP P450 enzymes in vivo.

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

13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Long-term studies have been completed to evaluate the carcinogenic potential of oxymorphone in both Sprague-Dawley rats and CD-1 mice. Oxymorphone HCl 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. The systemic drug exposure (AUC ng•h/mL) at the 10 mg/kg/day in male rats was 0.34-fold and at the 25 mg/kg/day dose in female rats was 1.5-fold the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in rats. Oxymorphone was administered to CD-1 mice (10, 25, 75 and 150 mg/kg/day) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 150 mg/kg/day dose in mice was 14.5-fold (in males) and 17.3-fold (in females) times the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in mice.

Mutagenesis
Oxymorphone hydrochloride was not mutagenic when tested in the in vitro bacterial reverse mutation

assay (Ames test) at concentrations of less than or equal to 5270 g/plate, or in an in vitro mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes at concentrations less than or equal to 5000 g/ml with or without metabolic activation. 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 greater than or equal to 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
Oxymorphone hydrochloride did not affect reproductive function or sperm parameters in male rats at any dose tested (less than or equal to 50 mg/kg/day). The highest dose tested is ~6-fold the human dose of 40 mg every 12 hours, based on body surface area. 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 doses of oxymorphone greater than or equal to 10 mg/kg/day. The dose of oxymorphone associated with reproductive findings in female rats is 1.2-fold the human dose of 40 mg every 12 hours based on a body surface area. The dose of oxymorphone that produced no adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

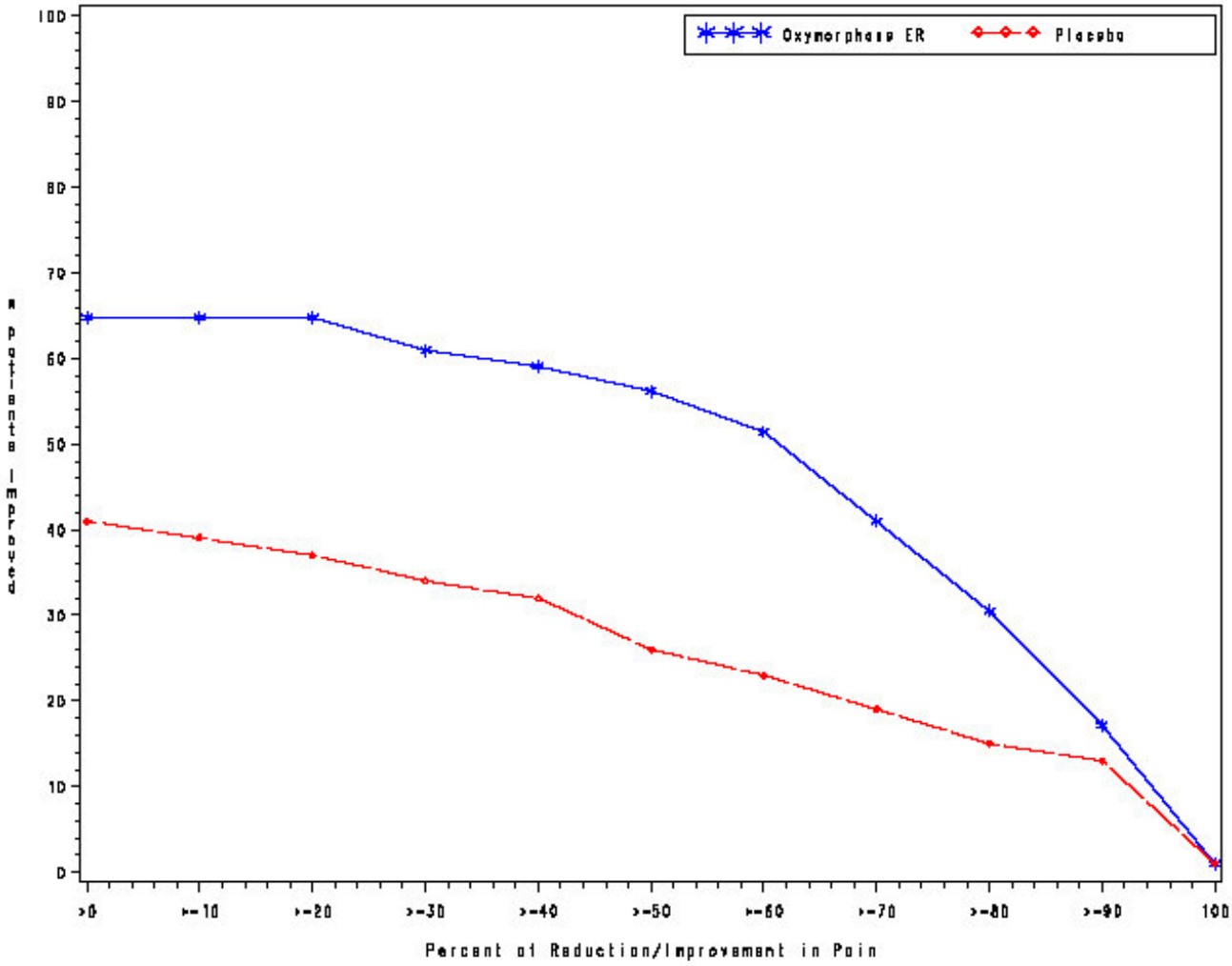
14 CLINICAL STUDIES 14.1 12-Week Study in Opioid-Naïve Patients with Low Back Pain 14.2 12-Week Study in Opioid-Experienced Patients with Low Back Pain

14 CLINICAL STUDIES
The efficacy and safety of OPANA ER 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.

14.1 12-Week Study in Opioid-Naïve Patients with Low Back Pain
Patients with chronic low back pain who were suboptimally responsive to their current non-opioid therapy entered a 4-week, open-label dose titration phase. Patients initiated therapy with two days of treatment with OPANA ER 5 mg, every 12 hours. Thereafter, patients were titrated to a stabilized dose, at increments of 5-10 mg every 12 hours every 3-7 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 OPANA ER. The mean±SD stabilized doses were 39.2±26.4 mg and 40.9±25.3 mg for the OPANA ER and placebo groups, respectively; total daily doses ranged from 10-140 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 OPANA ER completed the 12-week treatment compared to forty seven percent of patients treated with placebo. OPANA ER provided superior analgesia compared to placebo. The analgesic effect of OPANA ER 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 less than or equal to 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

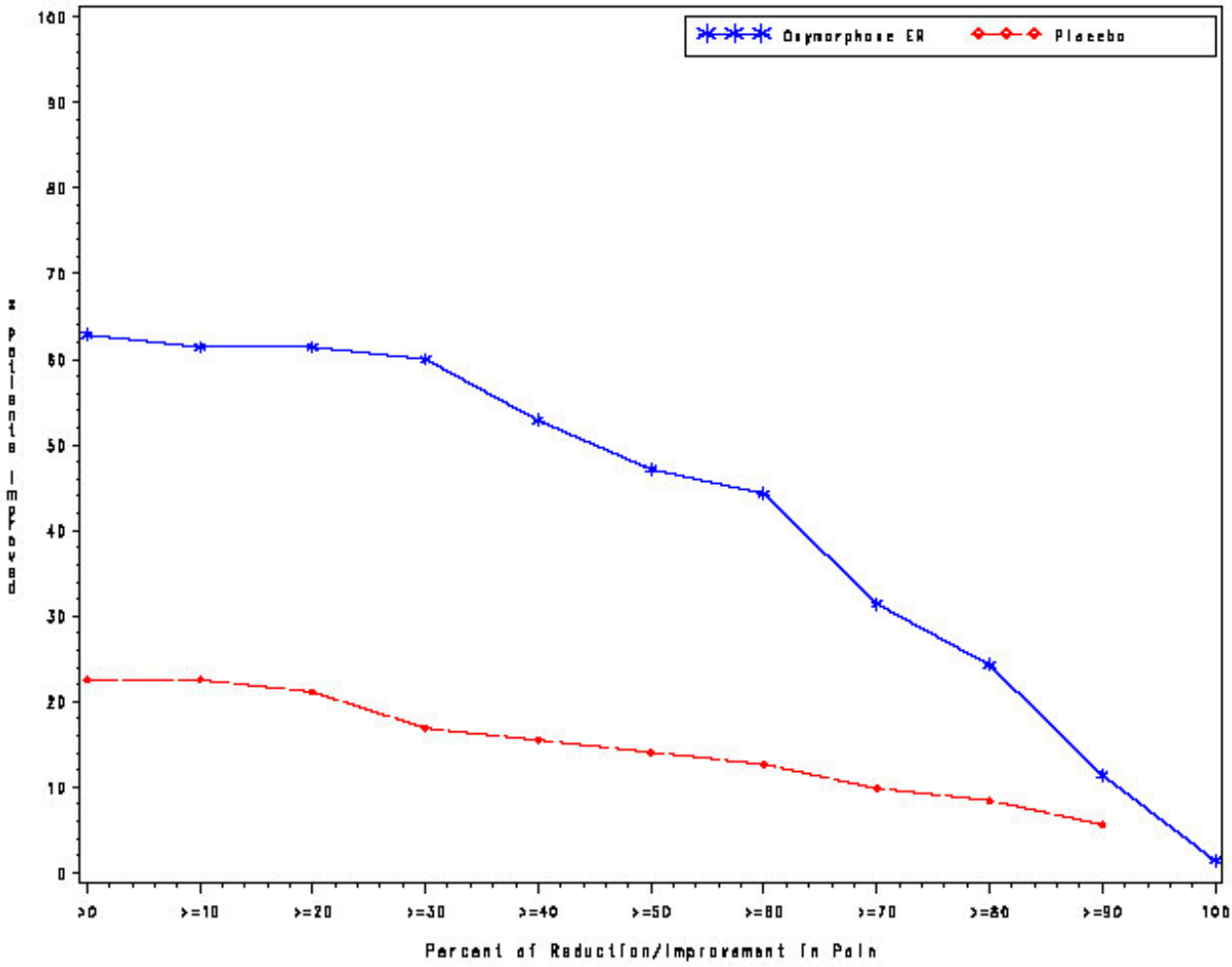


14.2 12-Week Study in Opioid-Experienced Patients with Low Back Pain

Patients currently on chronic opioid therapy entered a 4-week, open-label titration phase with OPANA ER 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 OPANA ER. The mean±SD stabilized doses were 80.9±59.3 mg and 93.3±61.3 mg for the OPANA ER 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 OPANA ER dose titration. Seventy percent of patients treated with OPANA ER and 26% of patients treated with placebo completed the 12-week treatment. OPANA ER provided superior analgesia compared to placebo. The analgesic effect of OPANA ER 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 less than or equal to 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



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

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

Advise patients to dispose of any unused tablets from a prescription by flushing them down the toilet as soon as they are no longer needed [see Patient Counseling Information (17)].

17 PATIENT COUNSELING INFORMATION

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

- Advise patients that OPANA ER contains oxymorphone, a morphine-like pain reliever, and should be taken only as directed.

- Advise patients that OPANA ER is designed to work properly only if swallowed whole. The extended-release tablets may release all their contents at once if broken, chewed or crushed, resulting in a risk of fatal overdose 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.

- Appropriate pain management requires changes in the dose to maintain best pain control. Advise patients of the need to contact their physician if pain control is inadequate, but not to change the dose of OPANA ER without consulting their physician.

- Advise patients to report episodes of breakthrough pain and adverse experiences occurring during therapy to their doctor. Individualization of dosage is essential to make optimal use of this medication.

- Caution patients that OPANA ER may cause drowsiness, dizziness, or lightheadedness, and may impair mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car, operating machinery, etc.

- Instruct patients not to combine OPANA ER with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because additive effects may occur, resulting in serious injury or death.

- Advise patients taking OPANA ER of the potential for severe constipation. Appropriate laxatives and/or stool softeners and other therapeutic approaches may be considered for use with the initiation of OPANA ER therapy.

- Advise patients not to adjust the dose of OPANA ER without consulting the prescribing professional.

- Advise patients that OPANA ER is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.

- Advise women of childbearing potential who become, or are planning to become pregnant to consult their physician regarding the effects of opioid analgesics and other drug use during pregnancy on themselves and their unborn child.

- If patients have been receiving treatment with OPANA ER for more than a few days to weeks and cessation of therapy is indicated, counsel them on the importance of safely tapering the dose and that abruptly discontinuing the medication could precipitate withdrawal symptoms. Provide patients with a dose schedule to accomplish a gradual discontinuation of the medication.

- As with any potent opioid, misuse of OPANA ER may result in serious adverse events. Instruct patients to keep OPANA ER in a secure place out of the reach of children and pets. Accidental consumption especially in children can result in overdose or death. When OPANA ER is no longer needed, instruct patients to destroy unused tablets by flushing them down the toilet.

FDA – Approved Patient Labeling

OPANA® ER (Ō-pan-a)
(Oxymorphone Hydrochloride) Extended-Release Tablets, CII

OPANA ER Tablets, 5 mg
OPANA ER Tablets, 7.5 mg

OPANA ER Tablets, 10 mg
OPANA ER Tablets, 15 mg
OPANA ER Tablets, 20 mg
OPANA ER Tablets, 30 mg
OPANA ER Tablets, 40 mg

IMPORTANT: Keep OPANA ER in a safe place away from children. Accidental use by a child is a medical emergency and can result in death. If a child accidentally takes OPANA ER, get emergency help right away.

Read the Patient Information that comes with OPANA ER before you start taking it and each time you get a new prescription. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. Share the important information in this leaflet with members of your household.

What Is the Most Important Information I Should Know About OPANA ER?

- OPANA ER can cause trouble breathing (hypoventilation), which can lead to death, if used differently than the way you were told to use it by your healthcare provider (see “What are the possible side effects of OPANA ER?”).

- Swallow OPANA ER tablets whole. Do not break, crush, dissolve, or chew OPANA ER tablets before swallowing. If a tablet is broken, crushed, dissolved, or chewed, the full 12 hour dose can be taken into your body all at once. This is very dangerous. You could die from an overdose of the medicine. Use OPANA ER exactly the way your healthcare provider prescribes. If you cannot swallow tablets whole, tell your healthcare provider. You may need a different medicine.

- Do not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while taking OPANA ER.

What is OPANA ER?
- OPANA ER is a prescription medicine that contains the opioid (narcotic pain medicine) oxymorphone. OPANA ER is used to treat adults with constant pain (around the clock) that is moderate to severe and is expected to last for an extended period of time. OPANA ER is not for occasional (—as needed) use.

- OPANA ER can cause physical dependence. Do not stop taking OPANA ER all of a sudden if you have been taking it for more than a few days. You could become sick with uncomfortable withdrawal symptoms because your body has become use to the medicine. Talk to your healthcare provider about slowly stopping OPANA ER to avoid getting sick with withdrawal symptoms. Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.

- OPANA ER is a controlled substance (CII) because it contains a narcotic painkiller that can be a target for people who abuse prescription medicines or street drugs. Keep your tablets in a safe place to protect them from being stolen. Never give your tablets to anyone else, even if they have the same symptoms you have. Selling or giving away this medicine may harm others, even causing death, and is against the law.

Who Should Not Take OPANA ER?
Do not take OPANA ER if:

- You had surgery within the past day (24 hours) and you were not taking OPANA ER before your surgery.

- Your pain is mild or will go away in a few days.

- Your pain can be controlled by the occasional use of other pain medicines.

- You are having an asthma attack or have severe asthma, trouble breathing, or lung problems.

- You have liver problems.

- You are allergic to OPANA ER or anything in it. See the end of this leaflet for a complete list of ingredients in OPANA ER.

- You have had severe allergic reactions to other narcotic pain medicines (such as morphine or codeine medicines). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.

OPANA ER is not for children under 18 years of age.

What Should I Tell My Healthcare Provider Before Starting OPANA ER?
Tell your healthcare provider about all of your medical problems, especially if you:

- have trouble breathing or lung problems

- have a head injury or brain problems

- have liver or kidney problems

- have adrenal gland problems, such as Addison's disease

- have convulsions or seizures

- have thyroid problems

- have problems urinating or prostate problems

- have pancreas problems

- have a drinking problem or alcoholism

- have severe mental problems or hallucinations (see or hear things that are not really there)

- have past or present drug abuse or drug addiction problems

- are pregnant or plan to become pregnant. OPANA ER may harm your unborn baby.

- are breastfeeding. OPANA ER may pass through your milk and may harm your baby. You should not breastfeed while taking OPANA ER.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may cause serious problems when taken with OPANA ER, especially if they cause sleepiness (like sleeping pills, anxiety medicines, antihistamines, or tranquilizers).

Do not take any new medicines while using OPANA ER until you have talked to your healthcare

provider or pharmacist and they have told you it is safe.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist.

How Should I Take OPANA ER?
- Follow your healthcare provider's directions exactly. Your healthcare provider may change your dose based on your reactions to the medicine. Do not change your dose unless your healthcare provider tells you to change it. Do not take OPANA ER more often than prescribed.

- Swallow OPANA ER tablets whole. Do not break, crush, dissolve, or chew OPANA ER tablets before swallowing. If a tablet is broken, crushed, dissolved, or chewed, the full 12 hour dose can be taken into your body all at once. This is very dangerous. You could die from an overdose of the medicine. If you cannot swallow tablets whole, tell your healthcare provider. You may need a different medicine.

- Take OPANA ER every 12 hours or as instructed by your healthcare provider. OPANA ER should be taken on an empty stomach, at least one hour before or two hours after meals. Talk to your healthcare provider if you feel sick taking OPANA ER on an empty stomach.

- If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your healthcare provider tells you to. If you are not sure about your dosing call your healthcare provider.

- If you take too much OPANA ER or overdose, call your local emergency number or poison control center right away.

- Talk to your healthcare provider often about your pain. Your healthcare provider can decide if you still need OPANA ER.

- If you have side effects that bother you or if you continue to have pain, call your healthcare provider.

- Stopping OPANA ER. If your healthcare provider decides you no longer need OPANA ER, ask how to slowly reduce the dose of your medicine so you don't get uncomfortable (withdrawal) symptoms such as nausea, sweating, and pain. You should not stop taking OPANA ER all at once if you have been taking it for more than a few days without talking to your healthcare provider. OPANA ER can cause physical dependence. You can get sick with withdrawal symptoms if you stop OPANA ER all at once, because your body has become use to it.

After you stop taking OPANA ER, flush the unused tablets down the toilet. Safely dispose of OPANA ER out of the reach of children and pets.

What Should I Avoid While Taking OPANA ER?
- Do not drive, operate heavy machinery, or participate in any other possibly dangerous activities until you know how you react to this medicine. OPANA ER can make you sleepy. Ask your healthcare provider to tell you when it is okay to do these activities.

- Do not drink alcohol while using OPANA ER. It may increase the chance of having dangerous side effects including overdose and death.

What are the Possible Side Effects of OPANA ER?
OPANA ER can cause trouble breathing.
Call your healthcare provider or get medical help right away if:

- your breathing slows down

- you have shallow breathing (little chest movement with breathing)

- you feel faint, dizzy, confused, or have any other unusual symptoms

These can be signs that you have taken too much OPANA ER (overdose) or the dose is too high for you, which can be dangerous and lead to death if not treated.

OPANA ER can cause your blood pressure to drop. This can make you feel dizzy if you get up too fast from sitting or lying down. Low blood pressure is also more likely to happen if you are taking other medicines that can also lower your blood pressure.

OPANA ER can cause physical dependence. Your body will get used to OPANA ER if you take it more than a few days. You can get sick with withdrawal symptoms if you stop taking OPANA ER all at once. You can avoid getting sick with withdrawal symptoms by stopping OPANA ER slowly. Your healthcare provider will tell you how to do this.

There is a chance of abuse or addiction with OPANA ER. Abuse or addiction is different than a physical dependence. If you have abused prescription medicines, street drugs or alcohol in the past, you may have a higher chance of developing abuse or addiction again while using OPANA ER. If you have more concerns, talk to your healthcare provider for more information about abuse and addiction.

The most common side effects of OPANA ER are nausea, constipation, dizziness, vomiting, itching, sleepiness, headache, increased sweating, and sedation. Some of these side effects may decrease with continued use. Talk to your healthcare provider if you continue to have these side effects.

These are not all the possible side effects of OPANA ER. For a complete list, ask your healthcare provider or pharmacist.

Constipation (decrease in the usual number of hard bowel movements) is a common side effect of opioid medicines, including OPANA ER. Talk to your healthcare provider or pharmacist about the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking OPANA ER.

How should I store OPANA ER?
- Store OPANA ER at room temperature between 59 to 86F (15to 30C).

- Keep OPANA ER in a childproof container and store in a safe place to protect it from being stolen.

- Keep OPANA ER out of the reach of children. Accidental overdose in children is an emergency and can result in death.

General Information about OPANA ER
- Do not use OPANA ER for conditions for which it was not prescribed.

- Do not give OPANA ER to other people, even if they have the same symptoms you have. It may harm them, even causing death, and it is against the law.

This leaflet summarizes the most important information about OPANA ER. If you would like more information, talk with your healthcare provider. Also, you can ask your pharmacist or healthcare provider for information about OPANA ER that is written for healthcare professionals.

What are the ingredients in OPANA ER?
Active Ingredient: oxymorphone hydrochloride

Inactive Ingredients: hypromellose, methylparaben, silicified microcrystalline cellulose, sodium stearyl fumarate, TIMERx®-N, titanium dioxide, and triacetin. The 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg tablets also contain macrogol, and polysorbate 80. 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 FDandC yellow No. 6. The 20 mg tablets contain FDandC blue No. 1, FDandC yellow No. 6, and DandC yellow No. 10. The 40 mg tablets contain FDandC yellow No. 6, DandC yellow No.10, and lactose monohydrate.

CAUTION: Federal law prohibits dispensing without prescription.

TIMERx®-N is a registered trademark of Penwest Pharmaceuticals Co., Danbury, Connecticut and is used herein pursuant to a license agreement between Penwest and Endo Pharmaceuticals.

2005648 / September 2010

Opana ER 20mg (CII) Tablet

OPANA ER
oxymorphone hydrochloride tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63629-4174(NDC:63481-617)
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
OXYMORPHONE HYDROCHLORIDE (UNII: 5Y2EI94NBC) (OXYMORPHONE - UNII:9VXA968E0C)	OXYMORPHONE HYDROCHLORIDE	20 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSES (UNII: 3NXW29V3WO)	
METHYLPARABEN (UNII: A2I8C7HI9T)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SODIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIACETIN (UNII: XHX3C3X673)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	

Product Characteristics

Color	green (GREEN)	**Score**	no score
Shape	OCTAGON (8 sided)	**Size**	8mm
Flavor		**Imprint Code**	20
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63629-4174-1	60 in 1 BOTTLE		
2	NDC:63629-4174-2	30 in 1 BOTTLE		
3	NDC:63629-4174-3	90 in 1 BOTTLE		
4	NDC:63629-4174-4	56 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021610	12/31/2010	

Labeler - Bryant Ranch Prepack (171714327)

Registrant - Bryant Ranch Prepack (171714327)

Establishment

Name	Address	ID/FEI	Business Operations

Bryant Ranch Prepack		171714327	REPACK(63629-4174) , RELABEL(63629-4174)