NDA 201655

OPANA® ER (Oxymorphone Hydrochloride Extended-Release Tablets)

Opioid Analgesic

ENDO Pharmaceuticals Inc.
100 Endo Boulevard
Chadds Ford, PA 19317
Telephone: (800) 462-3636

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

The goals of the OPANA ER REMS are:

1. To inform patients and healthcare professionals about the potential for abuse, misuse, overdose and addiction associated with the use of OPANA ER

2. To inform patients and healthcare professionals about the safe use of OPANA ER

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each OPANA ER prescription in accordance with 21 CFR 208.24.

The Medication Guide is part of the REMS and is appended.

B. Elements to Assure Safe Use

1. Healthcare professionals (HCP) who prescribe OPANA ER will receive training.

Reference ID: 3056370

a. Endo will ensure that training will be provided to HCPs who prescribe OPANA ER. Endo will ensure that each prescriber will be provided with the OPANA ER REMS educational material.

b. The OPANA ER REMS training includes the following:

   i. Proper patient selection
   ii. Appropriate OPANA ER dosing and administration
   iii. General opioid use including information about opioid abuse and how to identify patients who are at risk for addiction
   iv. The risks of abuse, misuse, overdose, and addiction from exposure to opioids, including OPANA ER
   v. Risks of OPANA ER, including:
      1. The risk of overdose caused by exposure to an essentially immediate-release form of oxymorphone by consuming broken, chewed, crushed or dissolved OPANA ER tablets
      2. The risk of addiction from exposure to OPANA ER
   vi. Information to counsel patients on the need to store opioid analgesics safely out of the reach of children and household acquaintances
   vii. The importance of providing each patient with a Medication Guide, instructing the patient to read the Medication Guide and assisting the patient in understanding the content.

c. Endo will ensure that at least 3 weeks prior to first availability of OPANA ER to healthcare professionals, a Dear Healthcare Professional letter will be mailed to HCPs experienced in treating chronic pain with opioid agonists, including pain specialists and primary care physicians. This letter is designed to convey and reinforce the risks of abuse, misuse, overdose, and addiction of OPANA ER, as well as the need to complete the OPANA ER REMS prescriber training. The letter will be available on the OPANA ER REMS website (www.OPANAERrems.com) for 1 year from the date of mailing.

d. The Dear Healthcare Professional letter mailing will include the following materials:

   i. Full Prescribing Information
   ii. Medication Guide
   iii. OPANA ER Healthcare Professional (HCP) Training Guide
   iv. OPANA ER REMS Education Confirmation Form

Reference ID: 3056370

e. Additional copies of the printed REMS materials will be available for download via the OPANA ER website (www.OPANAERrems.com) or by calling Endo's toll-free phone number 1-800-462-3636.
f. Endo will maintain a list of all prescribers who have completed the OPANA ER REMS training.

Prescribers will be re-trained every two years or following substantial changes to the OPANA ER REMS. Substantial changes may include changed to the OPANA ER Full Prescribing Information or to the Medication Guide that require substantial modification of the REMS educational materials.

The following materials are part of the REMS and are appended:

- Medication Guide
- Dear Healthcare Professional letter
- OPANA ER Healthcare Professional (HCP) Training Guide
- OPANA ER REMS Website
- OPANA ER REMS Education Confirmation Form

C. Implementation System

Because OPANA ER can be approved without the Elements to Assure Safe Use described under FDCA 505-1(f)(3)(B), (C), and (D) of the Act, an Implementation System is not required.

D. Timetable for Submission of Assessments

Endo will submit REMS assessments to the FDA every 6 months for the first year from the date of approval of the REMS and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment time interval. Endo will submit each assessment so that it will be received by the FDA before or on the due date.

Reference ID: 3056370

DEAR HEALTHCARE PROFESSIONAL LETTER

Reference ID: 3056370

[*COMPANY OR OPANA ER LOGO*]

[*DATE*]

Dear Prescriber:

The purpose of this communication is to notify you that a Risk Evaluation and Mitigation Strategy (REMS) has been instituted for OPANA® ER (oxymorphone HCl extended-release tablets). This REMS is required by the U.S Food and Drug Administration (FDA) to ensure that the benefits of OPANA ER outweigh the potential risks of abuse, misuse, overdose and addiction.

OPANA ER is a Schedule II controlled substance that contains oxymorphone, 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.

OPANA ER is NOT intended for use as "prn" (as needed) analgesic. OPANA ER is not indicated for treating acute or postoperative pain, mild pain, or pain that is not expected to persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate.

OPANA ER is contraindicated in patients who have:

- known hypersensitivity to any of its components or the active ingredient, oxymorphone or with known hypersensitivity to morphine analogs such as codeine
- significant respiratory depression
- acute or severe bronchial asthma, or hypercarbia (in unmonitored settings, or the absence of resuscitative equipment)
- or are suspected of having paralytic ileus
- moderate and severe hepatic impairment

Endo Pharmaceuticals has developed an FDA approved OPANA ER REMS educational program. The educational program components include Prescribing Information, the Medication Guide, and a *Healthcare Professional Training Guide*.

It is important that you read and understand the content of the educational material prior to prescribing OPANA ER. These materials are enclosed and are available online at www.OPANAERrems.com.

Reference ID: 3056370

Also enclosed is an Education Confirmation Form. **Please fill out the form to confirm that you have read the REMS Education Materials for OPANA ER and understand the major risks associated with OPANA ER and how to appropriately select and educate patients to whom OPANA ER is prescribed. Please answer the questions to verify your understanding of the information contained in the REMS Education Materials for OPANA ER.** Completion of the questions in the form does not affect your ability to prescribe OPANA ER. You may also complete the form online at www.OPANAERrems.com or via fax at 1-877-637-2039.

It is also important that you discuss the risks of OPANA ER with your patients and their caregivers. Encourage them to read the Medication Guide (see enclosed copy) that provides important information on the safe and effective use of OPANA ER. The Medication Guide will be provided to patients with each prescription.

Additional copies of the Medication Guide are available by download from www.OPANAERrems.com or by contacting our Call Center at 1-800-462-3636.

Please report all suspected adverse events associated with the use of OPANA ER to 1-800-462-3636.

Adverse event information may also be reported to the FDA MedWatch Reporting System by phone at 1-800-FDA-1088 (1-800-332-1088) or by mail using Form 3500 at www.fda.gov/medwatch.

Refer to the full Prescribing Information, with the boxed warning, for detailed safety information for OPANA ER. Educational information on OPANA ER is available at www.OPANAERrems.com.

Sincerely,
[*NAME*]
[*TITLE*]

Enclosures:
OPANA ER Medication Guide
OPANA ER Prescribing Information

Reference ID: 3056370

OPANA ER Healthcare Professional Training Guide
OPANA ER Education Confirmation Form

This letter was approved by the Food and Drug Administration as part of the OPANA ER REMS.

Reference ID: 3056370

Reference ID: 3056370

HEALTHCARE PROFESSIONAL TRAINING GUIDE

Cover

(HEADLINE) **PRESCRIBING OPANA® ER - CII**

(Subhead) Healthcare Professional Training Guide
[*COMPANY OR OPANA ER LOGO*]

Reference ID: 3056370

Page 2

(HEADLINE) **IMPORTANT SAFETY INFORMATION**

(Box 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.

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.

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.

Limitations of Use

OPANA® ER is NOT intended for use as an as needed analgesic.

OPANA® ER tablets are to be swallowed whole and are not to be cut, broken, chewed, dissolved, or crushed. Taking cut, 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.

Reference ID: 3056370

Page 3

(HEADLINE) **INTRODUCTION**

(Copy) This Risk Evaluation and Mitigation Strategy (REMS) has been created to educate prescribers, patients, and caregivers about the potential risks associated with OPANA ER, which are reflected in the goals of the REMS.

1: To inform patients and healthcare professionals about the potential for abuse, misuse, overdose and addiction associated with the use of OPANA ER.

2: To inform patients and healthcare professionals about the safe use of OPANA ER.

The purpose of this training guide is to provide prescribers with important safety information about OPANA ER so they can prescribe and counsel patients appropriately about the potential risks of OPANA ER abuse, misuse, overdose and addiction. Refer to the full Prescribing Information for complete safety information for OPANA ER.

You should individualize treatment in every case using a progressive plan of pain management such as that outlined by the World Health Organization, the Federation of State Medical Boards Model Policy, and the American Pain Society. Healthcare providers should follow appropriate pain management principles of careful assessment and ongoing monitoring.

In addition, patients and their caregivers must be told to carefully read the *OPANA® ER Medication Guide*. This Medication Guide contains important information to ensure the safe and appropriate use of OPANA ER, and to help prevent abuse, misuse, addiction and overdose.

Finally, it is critical that you counsel patients and their caregivers about the need to store OPANA ER out of the reach of children, household visitors and pets, in a safe and secure place. This will help reduce the risk of an accidental overdose, which may result in death.

Following your review of the enclosed information, please complete and return to Endo Pharmaceuticals the Education Confirmation Form to verify your understanding of the information contained in the REMS Education Materials. The REMS materials and Education Confirmation Form can be obtained online at www.OPANAERrems.com or by calling 1-800-462-3636. Completion of the form and questions does not affect your ability to prescribe OPANA ER.

Reference ID: 3056370

Page 4

(HEADLINE) **TABLE OF CONTENTS**

(Copy)

Risks of Overdose

Risk of Respiratory Depression

Interaction with Alcohol and other CNS Depressants

Additional Side Effects

Risks of Abuse, Misuse, and Addiction

Addictive Disorder vs. Physical Dependence

Screening for Patients at Risk for Opioid Abuse or Addiction

Proper Patient Selection

Appropriate Dosing and Administration

- Starting Therapy
- Individualizing Dosage
- Continuing Therapy
- Stopping Therapy

What You Need To Tell Patients about OPANA® ER

References

(HEADLINE) **RISKS OF OVERDOSE WITH OPANA® ER**

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

Following is important information about overdose risks with OPANA ER. Refer to the full Prescribing Information for complete information about OPANA ER overdose.

(Subhead) Risk of Overdose from Intact Tablets

Any person who has not developed tolerance to the respiratory depressant or sedating effects of OPANA ER is at risk for overdose from exposure to inappropriate doses of OPANA ER, especially with concomitant exposure to drugs that depress respiratory drive or consciousness, whether there is a legitimate need for an analgesic or not.

(Subhead) Risk of Overdose from Alteration of Tablets

(Copy) **OPANA ER tablets must be swallowed whole and must not be cut, broken, chewed, dissolved, or crushed. Taking cut, broken, chewed, dissolved, or crushed OPANA ER tablets leads to rapid release and absorption of a potentially fatal dose of oxymorphone.**

The risk of a fatal overdose is even greater when OPANA ER is abused together with alcohol, prescription and non-prescription medications containing alcohol, including other opioids, and other CNS depressants. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and potentially fatal overdose of oxymorphone.

(Subhead) Risk of Overdose from Higher Doses

(Copy) Patients can overdose by taking just one dose of OPANA ER.

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

Page 6

(HEADLINE) **Risk of Respiratory Depression**

(Copy) Respiratory depression is the chief hazard associated with OPANA ER and can result in death.

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.

Page 7

(HEADLINE) **Interactions with Alcohol and other CNS Depressants**

(Copy) 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. Avoid concurrent use of alcohol and OPANA ER.

Page 8

(HEADLINE) **ADDITIONAL SIDE EFFECTS**

(Copy) Adverse reactions reported in placebo-controlled clinical trials with incidence >= 2% receiving oxymorphone hydrochloride extended-release tablets include nausea, constipation, dizziness, somnolence, vomiting, pruritus, headache, sweating, increased dry mouth, sedation, diarrhea, insomnia, fatigue, appetite decreased and abdominal pain.

The common (>=1% to <10%) adverse drug reactions reported at least once by patients treated with oxymorphone hydrochloride extended-release tablets in the clinical trials include eye disorders, gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders, psychiatric disorders, respiratory, thoracic and mediastinal disorders and vascular disorders.

Refer to the full Prescribing Information, Warnings and Precautions and Adverse Reactions sections for a comprehensive list of adverse events for oxymorphone hydrochloride extended-release tablets.

Page 9

(HEADLINE) **RISKS OF ABUSE, MISUSE, AND ADDICTION**

(Subhead) OPANA ER has an Abuse Liability Similar to Morphine

(Copy) OPANA ER contains oxymorphone, a mu 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.

All patients treated with OPANA ER and other 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.

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.

(Subhead) Addiction to OPANA ER is Possible

(Copy) There is a potential for drug addiction to develop following exposure to OPANA ER, even during appropriate medical use.

People who have abused prescription medications in the past may have a higher chance of abusing or developing addiction again when treated with OPANA ER.

Behaviors that suggest drug abuse exist on a continuum, and pain-relief seeking behavior can be mistaken for drug-seeking behavior. All patients treated with OPANA ER require careful monitoring for signs of addiction and drug abuse.

Reference ID: 3056370

Page 10

(HEADLINE) **ADDICTIVE DISORDER VS. PHYSICAL DEPENDENCE**

(Copy) It is important to differentiate between a person with an addiction disorder and a patient with pain who is adherent to therapy and has developed a physical dependence on opioid analgesic medications.

(Subhead) Patients With Addiction Disorders:[1]

- Suffer from a chronic, neurobiologic disease with genetic, psychosocial, and environmental components
- Seek a drug in order to quickly affect the "reward center" of their brains
- Crave drugs and use them compulsively
- Continue abuse despite negative, even life-threatening, physical, mental, and/or social consequences
- These persons often develop physical dependence to the substances they are abusing and are, therefore, at risk for signs and symptoms of withdrawal syndrome upon exposure to an antagonist (in the case of physical dependence on an opioid or benzodiazepine), significant reduction in dose or abrupt cessation of administration of the drug

(Subhead) Patients With Physical Dependence Who Do Not Have an Addiction Disorder:[1]

- Experience a normal response to the ongoing use of certain medicines, including opioids
- Want sufficient medicine to reach opioid receptors to induce analgesia
- Take medicines to relieve pain—not to satisfy a craving for a psychic effect or to stave off withdrawal syndrome
- Can generally discontinue their medicine with mild to no withdrawal syndrome once their symptoms are gone by gradually tapering the dosage according to their doctor's orders

Reference ID: 3056370

Pages 11

(HEADLINE) **SCREENING FOR PATIENTS AT RISK FOR OPIOID ABUSE OR ADDICTION**

(Copy) Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed an opioid, and all patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction.

(Subhead) Patient/Family History

(Copy) Persons at increased risk for opioid abuse include those with a personal or family history of substance use disorder (including drug or alcohol abuse or addiction) or mental illness (eg, major depression).

Participation or recommended participation in drug abuse treatment programs should be determined. Patients who have undergone opioid detoxification in the past are at higher risk for re-emergence of substance use disorders.

(Subhead) Screening Tests and Physical Appearance

(Copy) Many drug abuse screening tests have been developed for use in clinical practice, including the CAGE and CAGE-AID Questionnaire, the Addiction Behaviors Checklist, the Opioid Risk Tool, The Brief MAST, and the Two-Item Conjoint Screening (TICS) for Alcohol & Other Drug Problems.[2,3]

Physical screening may reveal signs of possible drug abuse. Initial screening clues may include unkempt appearance, ill-fitting clothes suggestive of weight loss/gain, sniffles, watery eyes, cough, nausea; lethargy, drowsiness, and nodding. Careful examination of skin may reveal marks caused by repeated injections.[4]

While these signs might suggest abuse, they should not be the only criteria for determining whether opioid abuse has occurred.

Reference ID: 3056370

(Subhead) Laboratory Tests

(Copy) Laboratory signs that may suggest substance abuse include elevated mean corpuscular volume (MCV) and abnormal liver enzymes.[2,3]

Urine drug testing may yield unexpected results. The use of this technology requires understanding of specificity and sensitivity of the particular analytic method employed. Some point-of-care urine tests for "opioids" or "opiates" do not, for example, detect semisynthetic or synthetic opioid analgesics.[2,5]

All laboratory markers are nonspecific for alcohol or drug use and should be viewed as screens, not as diagnostic criteria.

(Subhead) Other Signs

(Copy) Signs of compulsive drug use include covertly obtaining prescription medications from more than one physician, referred to as "Doctor Shopping," concurrent abuse of related illicit drugs, altering or forging prescriptions, and repeated unsanctioned dose escalations despite warnings.

Other signs of compulsive drug use may be more subtle, including frequent visits to emergency rooms, and hoarding of drugs obtained from routine prescriptions.

Page 12

(HEADLINE) **SCREENING FOR PATIENTS AT RISK FOR OPIOID ABUSE OR ADDICTION (CONT'D)**

(Subhead) When You Suspect Addiction or Drug Abuse

(Copy) Following are some suggestions about what to do if you suspect a patient is addicted to, or abusing OPANA ER:[6]

- Remember, a person abusing drugs or affected by addictive disorder is in need of treatment for that disorder and any concomitant medical or mental conditions they have, although self-administered opioid analgesics may not be indicated
- Refer the patient to an addiction specialist or substance use treatment center, if warranted
- If you are not the primary care physician, always consult a patient's regular physician before initiating treatment with an opioid analgesic
- Contact authorities if you are threatened in any way

Reference ID: 3056370

Pages 13

(HEADLINE) **PROPER PATIENT SELECTION**

(Bold Copy) **Careful patient selection is key to initiating the appropriate use of OPANA ER. The decision to use this opioid must balance the potential benefits with the risks of OPANA ER treatment. The following points should be reviewed when considering treatment for your patients.**

(Subhead) Who May Be Appropriate for Treatment with OPANA ER

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

As used here, "moderate to severe" pain does not include commonplace and ordinary aches and pains, pulled muscles, cramps, sprains, or similar discomfort. OPANA ER is not intended for use as an as needed analgesic.

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).

Please see full Prescribing Information (PI) including boxed warning.

Page 14

(HEADLINE) **PROPER PATIENT SELECTION (CONT'D)**

(Subhead) Some Patients Should Never Receive OPANA ER

(Copy) For some patients, the risks associated with OPANA ER therapy outweigh any potential benefits, and therefore, its use is contraindicated in such patient populations.

OPANA ER is contraindicated in:

- Patients who have significant respiratory depression
- Patients who have or are suspected of having paralytic ileus
- Patients who have acute or severe bronchial asthma, or hypercarbia
- Patients with moderate and severe hepatic impairment
- Patients with known hypersensitivity to any of OPANA ER's components or the active ingredient, oxymophone, or with known hypersensitivity to morphine analogs such as codeine.

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

Reference ID: 3056370

(Subhead) Assess for Risks of Opioid Abuse or Addiction before Starting Treatment With OPANA ER

(Copy) Patients should be assessed for risks of opioid abuse or addiction before they start treatment with OPANA ER. In addition to a complete medical history, a detailed history of alcohol and other substance use in the patient and family is important to establish before initiating treatment with OPANA ER.[2]

(Copy) Persons at increased risk for opioid abuse include those with a personal or family history of substance use disorders (including drug or alcohol abuse or addiction) or mental illness (eg, major depression).[2]

Documentation and maintenance of careful prescribing and treatment records is essential for supporting the evaluation, the reason for OPANA ER prescribing, the overall pain management plan, and any consultations received.[2] Documentation should include:

- Strength and quantity of the OPANA ER prescribed
- Dose and frequency of administration
- Timeliness of requests for another prescription
- Initial and ongoing assessment of patients' pain
- Proper prescribing practices
- Periodic reevaluation of all therapy prescribed or recommended, including progress toward established treatment goals.

Reference ID: 3056370

Pages 15

(HEADLINE) **APPROPRIATE DOSING AND ADMINISTRATION**

(Copy)

Initial doses should be low, especially in patients receiving concurrent treatment with muscle relaxants, sedatives, or other central nervous system (CNS) medications.

To avoid the risk of a potentially fatal dose, tablets must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved.

OPANA ER tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.

Administer OPANA ER on an empty stomach, at least one hour prior to or two hours after eating.

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. 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.

Start patients with mild hepatic impairment with the lowest dose and titrated slowly while carefully monitoring side effects. OPANA ER is contraindicated in patients with moderate or severe hepatic impairment.

Please see full Prescribing Information (PI) including boxed warning for complete Dosing and Administration Information.

(Subhead) Starting Therapy

(Copy) Physicians should initiate OPANA ER treatment only in patients who are at the appropriate point along the progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen, to OPANA ER, in a plan of pain management such as outlined by the World Health Organization, the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

Reference ID: 3056370

It is critical to initiate and adjust the dosing regimen for each patient individually, taking into account:

- Risk factors for abuse or addiction
- Age, general condition and medical status of the patient
- Current and anticipated pain intensity (eg, stable, increasing, decreasing)
- Patient's opioid exposure and degree of opioid tolerance (if any)
- Special instructions for patients who are not opioid experienced
- Major organ function that may affect absorption, distribution, metabolism or excretion of OPANA ER
- Pharmacokinetic and pharmacodynamic interactions with concomitant medications
- Incomplete cross-tolerance among opioid analgesics
- Genetic variability in pharmacokinetics or pharmacodynamics
- Balance between pain control and adverse reactions of OPANA ER

Page 16

(HEADLINE) **APPROPRIATE DOSING AND ADMINISTRATION (CONT'D)**

For patients who are new to opioid therapy
Please refer to full prescribing information for patients who are taking non-opioid analgesics and require continuous around-the-clock therapy for an extended period of time.

For patients who are NOT opioid-experienced (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.

For patients previously taking opioids
See full prescribing information for full details on converting from existing opioid therapy to OPANA ER therapy**.**

(Subhead) Individualizing Dosage

(Copy) After therapy is initiated, individually titrate each patient to a OPANA ER dose that provides an appropriate balance between pain relief and opioid-related side effects.

During periods of changing analgesic requirements, including initial titration, maintain frequent communication with other members of the healthcare team, your patient, and the caregiver/family.

(HEADLINE) **APPROPRIATE DOSING AND ADMINISTRATION (CONT'D)**

(Subhead) Continuing Therapy

(Copy) During chronic opioid therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (eg, every 6 to 12 months) as appropriate.

OPANA ER therapy should be reviewed and adjusted, taking into consideration the patient's own reports of pain and side effects and the health care provider's clinical judgment. OPANA ER should be individually titrated to a dose that provides an appropriate balance between analgesia and side effects. All patients treated with OPANA ER should be routinely monitored for signs of misuse, abuse, and addiction.

Please see full Prescribing Information (PI), including boxed warning.

(Subhead) Stopping Therapy

(Copy) When the patient no longer requires OPANA ER therapy, taper the dose gradually to prevent signs and symptoms of withdrawal in the physically-dependent patient.

(Copy) Please see full Prescribing Information (PI), including boxed warning and the OPANA® ER Medication Guide.

Page 17

(HEADLINE) **WHAT YOU NEED TO TELL PATIENTS ABOUT OPANA® ER**

(Copy) Once you have identified an appropriate patient for OPANA ER treatment, it is important to discuss the following information with the patient and/or their caregiver to ensure safe and appropriate use and disposal, and help to prevent misuse, abuse, and risk of overdose.

- **Patients and caregivers must be told to carefully read the OPANA ER Medication Guide that is provided with each prescription. It is extremely important to remind them that the important safety information in the OPANA® ER Medication Guide could have changed since their last OPANA ER prescription was filled**.

- Patients and caregivers should be told that OPANA ER contains oxymorphone and since oxymorphone first became available, there have been reports of misuse, abuse, overdose, and addiction in some people. So the patient needs to decide if he or she wants to use, or continue to use OPANA ER

- ***Also tell patients and caregivers:***

  1. Always follow the prescribing directions about OPANA ER *exactly* and never change the dose, the dosing frequency, or suddenly stop taking OPANA ER without consulting the doctor first.

2. Take OPANA ER only by mouth and swallow the tablets whole. Do not break, crush, dissolve, or chew them before swallowing as this can be very dangerous, causing an overdose, and possibly death.
3. OPANA ER may impair mental and/or physical ability required to perform potentially hazardous tasks (eg, driving, operating heavy machinery).
4. You should not combine OPANA ER with alcohol or other central nervous system depressants (eg, sedatives, hypnotics) because dangerous additive effects may occur, resulting in serious injury or death.
5. Women of childbearing potential who become, or are planning to become, pregnant should consult their doctor regarding the effects of OPANA ER and other drug use during pregnancy on themselves and their unborn child.
6. Keep OPANA ER away from children, household visitors and pets in a safe and secure place, such as locked box or cabinet. Accidental overdose by a child is dangerous and may result in death.
7. OPANA ER should not be stored in the bathroom medicine cabinet because bathroom medicine cabinets rarely lock, in the glove compartment of a car or in kitchen cabinets, inside purses, coat pockets, nightstands, or other locations easily accessed by others.
8. OPANA ER contains a drug that some people may want to abuse. OPANA ER should only be used by the patient who was prescribed it. A patient should protect his or her OPANA ER from being stolen.
9. Giving or selling OPANA ER to other people is very dangerous and against the law.
10. When OPANA ER is no longer needed, patients should flush unused tablets down the toilet. OPANA ER should not be discarded in the wastebasket where children or others can find it.
11. If a patient suspects that someone has stolen their OPANA ER, he or she should report the incident to the local police department.
12. Never take or give medicine in the dark. Patients should always turn the light on and wear their glasses if they need them for reading before taking or administering medication.
14. Use child-resistant packaging on medicines whenever possible.

- Caregivers should be told to check the label every time they give medicine to a loved one.

Please see full Prescribing Information (PI), including boxed warning and the OPANA® ER Medication Guide.

(HEADLINE) **REFERENCES**

(References)

1. American Pain Society. Definitions related to the use of opioids for the treatment of pain. Available at: http://www.ampainsoc.org/advocacy/opioids2.htm.

2. Chou R, Fanciullo GJ, Fine PG, et al; for the American Pain Society–American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113-130.

3. Ewing, JA. Detecting alcoholism: the CAGE questionnaire. *JAMA.1984;* 252 (14): 1905-1907.

4. The National Clearinghouse for Alcohol and Drug Information. Drug categories for substances of abuse. Available at: http://ncadi.samhsa.gov/govpubs/rpo926//.

5. Gourlay DL, Caplan YH, Heit HA. Urine drug testing in clinical practice: dispelling the myths and designing strategies. Available at: http://www.familydocs.org/files/udtmonograph.pdf.

6. Weaver MF, Jarvis MAE, Schnoll SH. Role of the primary care physician in problems of substance abuse. *Arch Intern Med*. 1999;159:913-924.

(Copy) Please see full Prescribing Information (PI), including boxed warning and *OPANA® ER Medication Guide*.

OPANA ER REMS WEBSITE

www.OPANAERrems.com

Reference ID: 3056370

Initial REMS Approval: 12/2011

Print | A A A

opana ER (oxymorphone HCl) EXTENDED-RELEASE TABLETS

Full Prescribing Information | Medication Guide | Education Program | Contact Us

Welcome to the Opana® ER Risk Evaluation and Mitigation Strategy Website

As required by the U.S. Food and Drug Administration, a Risk Evaluation and Mitigation Strategy (REMS) has been created to educate healthcare professionals about the potential risks associated with the use of Opana ER (oxymorphone HCl). The goals of the Opana ER REMS are: (1) to inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction with Opana ER, and (2) to inform patients and healthcare professionals about the safe use of Opana ER.

Please click here for full Prescribing Information

You may download the Opana® ER REMS information:

- Dear Healthcare Professional Letter
- Dear Pharmacist Letter
- Opana® ER Full Prescribing Information
- Opana® ER Medication Guide
- Healthcare Professional Training Guide

Education Confirmation Form »

Healthcare Professional Education Program: Training and REMS Information

The Opana® ER REMS requires that Opana ER should only be prescribed in accordance with the Opana ER REMS, including healthcare professional training on responsible prescribing and use.

The Opana ER REMS education can be completed in 3 steps.

1. **First,** read the Dear Healthcare Professional Letter that describes the goals of the Opana ER REMS and is designed to convey and reinforce risks of abuse, misuse, overdose, and addiction associated with Opana ER.
2. **Second,** read the Healthcare Professional Training Guide that is specifically designed to concisely describe the potential risks of abuse, misuse, overdose, and addiction from exposure to Opana ER.
3. **Third,** complete the Education Confirmation Form to acknowledge and verify your understanding of the safe use of Opana ER.

Opana ER 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.

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.

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.

Limitations of Use

Opana® ER is NOT intended for use as an as needed analgesic.

Opana® ER tablets are to be swallowed whole and are not to be cut, broken, chewed, dissolved, or crushed. Taking cut, 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.

Privacy/Legal | Site Map

Full Prescribing Information | Medication Guide | Education Program | Contact Us

ENDO PHARMACEUTICALS
CHADDS FORD, PENNSYLVANIA 19317

Rx Only

Intended for US Residents Only.

©2011 Endo Pharmaceuticals Inc. All rights reserved.

To obtain formulary information for Opana® ER, click here.

Opana® ER is a trademark of Endo Pharmaceuticals.

XXXXXXXX2011

Print | A A A

opana ER (oxymorphone HCl) EXTENDED-RELEASE TABLETS

Full Prescribing Information | Medication Guide | Education Program | Contact Us

Education Program

An education program has been developed to provide healthcare professionals with important safety information about Opana® ER tablets.

The Healthcare Professional training program consists of 3 steps:

1. First, read the Dear Healthcare Professional Letter that describes the goals of the Opana ER REMS and is designed to convey and reinforce risks associated with Opana ER.
2. Second, read the Healthcare Professional Training Guide that is specifically designed to concisely describe the potential risks of abuse, misuse, overdose, and addiction from exposure to Opana ER.
3. Third, complete the Education Confirmation Form to acknowledge and verify your understanding of the safe use of Opana ER.

You may download the Opana® ER REMS information:

- Dear Healthcare Professional Letter
- Dear Pharmacist Letter
- Opana® ER Full Prescribing Information
- Opana® ER Medication Guide
- Healthcare Professional Training Guide

Education Confirmation Form »

Opana ER 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.

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.

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.

Limitations of Use
Opana® ER is NOT intended for use as an as needed analgesic.

Opana® ER tablets are to be swallowed whole and are not to be cut, broken, chewed, dissolved, or crushed. Taking cut, 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.

Privacy/Legal | Site Map

Full Prescribing Information | Medication Guide | Education Program | Contact Us

ENDO PHARMACEUTICALS
CHADDS FORD, PENNSYLVANIA 19317

Rx Only

Intended for US Residents Only.
©2011 Endo Pharmaceuticals Inc. All rights reserved.
To obtain formulary information for Opana® ER, click here.
Opana® ER is a trademark of Endo Pharmaceuticals.
XXXXXXXX2011

OPANA ER REMS EDUCATION CONFIRMATION FORM

Reference ID: 3056370

Initial REMS Approval: 12/2011

OPANA® ER

(oxymorphone HCl extended-release) Tablets

Education Confirmation Form

Completion of this form does not affect your ability to prescribe OPANA® ER.

Please complete and submit this form electronically on www.OPANAERrems.com or via fax to 1-877-637-2039.

The purpose of this form is to confirm that you have read the REMS Education Materials for OPANA® ER and understand the major risks associated with OPANA® ER and how to appropriately select and educate patients to whom OPANA® ER is prescribed.

I attest that I have read and understand the REMS Education Materials for OPANA® ER.

Signature Date

Prescriber Name (Please Print) Professional Designation

Specialty

Affiliation (if any)

Address

City State Zip Code

Telephone # Fax #

E-mail Address

Reference ID: 3056370

Please answer the questions on the reverse side to verify your understanding of the information contained in the REMS Education materials. Completion of the questions does not affect your ability to prescribe OPANA® ER.

OPANA® ER

(oxymorphone HCl extended-release) Tablets

---

1. **Which of the following is the most significant serious adverse event risk with OPANA® ER?**

   □Heart attack □Constipation □Dizziness
   □Respiratory depression □Drowsiness

2. **Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed OPANA® ER. Which of the following persons are at increased risk of opioid abuse?**

   (Please check all that apply.)

   □Individuals who have low back pain

   □Individuals with a personal history of substance abuse

   □Individuals with a family history of substance abuse

   □Individuals with mental illness (eg, major depression)

   □Individuals with a family history of hypercholesterolemia

3. **OPANA® ER is 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.**

   □True □False

4. **Proper use of OPANA® ER involves the following: (Please check all that apply)**

   □Unused OPANA® ER should be stored indefinitely in unlocked cabinets

   □OPANA® ER must be swallowed whole

   □OPANA® ER must not be chewed or ingested after crushing, breaking, or dissolving

   □OPANA® ER must not be ingested with alcohol

   □None of the above

Reference ID: 3056370

5. **OPANA® ER needs to be stored in a secure place away from children, pets, and household visitors.**

   □True □False

6. **Which of the following statements are true regarding the proper dosing of OPANA® ER in opioid naïve patients? (Please check all that apply.)**

   □Use low initial doses, especially in patients who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS medications

   □When converting patients from a non-opioid analgesic 20 mg q12h is a reasonable starting dose

   □OPANA® ER dose adjustments may be made every 1-2 days

   □None of the above

7. **As a result of reviewing the information in the training guide, do you feel that you have sufficient information to counsel patients about the proper use, storage, and disposal of OPANA® ER?**

   □Yes □No

   If no, please visit www.OPANAERrems.com for information or contact Endo at 1-800-462-3636 with any questions or concerns.

Reference ID: 3056370

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BOB A RAPPAPORT
12/09/2011