Endo Statement On FDA Advisory Committees' Vote Related To OPANA® ER

March 15, 2017

DUBLIN, March 14, 2017 /PRNewswire/ -- Endo International plc (NASDAQ / TSX: ENDP) today announced that the U.S. Food and Drug Administration's (FDA) Drug Safety Risk Management and Anesthetic and Analgesic Drug Products Advisory Committees voted 18 to eight, with one abstention, that the benefits of reformulated OPANA® ER (oxymorphone hydrochloride extended release) no longer outweigh its risks. While several of the Advisory Committee members acknowledged the role of OPANA® ER in clinical practice, others believed its benefits are now overshadowed by the continuing public health concerns around the product's misuse, abuse and diversion. During the Advisory Committee discussion following the vote, a number of Committee members expressed their preference that OPANA® ER remain on the market with additional regulatory restrictions to mitigate the risks.

The FDA convened these Advisory Committees to discuss pre- and post-marketing data about the abuse of OPANA® ER, the product's overall risk-benefit profile, as well as the abuse of generic oxymorphone ER and oxymorphone immediate-release (IR) products. While the FDA will consider the Committees' vote, any decision regarding whether to take regulatory action rests solely with the Agency. Endo believes that OPANA® ER remains an important clinical choice for appropriate patients and will evaluate the range of available options for maintaining access for legitimate use.

"Endo remains confident that the body of evidence established through clinical research demonstrates that OPANA® ER has a favorable risk-benefit profile when used as intended in appropriate patients," said Matthew W. Davis, M.D., R.Ph., Senior Vice President, Research & Development, Branded Pharmaceuticals at Endo. "Our top priorities include patient safety and ensuring that patients with chronic pain have access to safe and effective therapeutic options. We plan to work collaboratively with the FDA as the Agency completes its evaluation of OPANA® ER, while advocating to preserve the important benefits of the medicine for patients."

Endo's Commitment to Reducing the Abuse and Diversion of Opioid Medications
As a responsible opioid manufacturer, Endo is committed to reducing the potential abuse, misuse and diversion of these products and has taken a number of efforts to date, including:

- Supporting initiatives with targeted interventions aimed at understanding IV abuse of opioids, including: parent coaching trainings; a pilot mobile texting parent support initiative; a toll-free hotline for families and patients; a media awareness campaign; increased law enforcement outreach; increased local treatment center outreach; and increased outreach with local community leaders;
- Conducting an ethnographic study aimed at better understanding the causes of IV abuse in the Tennessee region; and
- Implementing a product serialization project aimed at preventing product counterfeiting, tampering and diversion and protecting patient safety in compliance with the Federal Drug Supply Chain Security Act (DSCSA).

INDICATION

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

Limitations of Use

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

IMPORTANT SAFETY INFORMATION ABOUT OPANA® ER

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

INTERACTION WITH ALCOHOL; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

OPANA® ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing OPANA® ER, and monitor all patients regularly for the development of these behaviors and conditions.

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of OPANA® ER. Monitor for respiratory depression, especially

during initiation of OPANA® ER or following a dose increase. Instruct patients to swallow OPANA® ER tablets whole; crushing, chewing, or dissolving OPANA® ER tablets can cause rapid release and absorption of a potentially fatal dose of oxymorphone.

Accidental Ingestion

Accidental ingestion of even one dose of OPANA® ER, especially by children, can result in a fatal overdose of oxymorphone.

Neonatal Opioid Withdrawal Syndrome

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

Interaction with Alcohol

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

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

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

CONTRAINDICATIONS

OPANA® ER is contraindicated in patients with:

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

WARNINGS AND PRECAUTIONS
Addiction, Abuse, and Misuse

- OPANA® ER contains oxymorphone, a Schedule II controlled substance. Because extended-release products such as OPANA® ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxymorphone present.
- Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed
- OPANA® ER. Addiction can occur at recommended doses and if the drug is misused or abused.
- Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing OPANA® ER, and monitor all patients receiving OPANA® ER for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as OPANA® ER, but use in such patients necessitates intensive counseling about the risks and proper use of OPANA® ER, along with intensive monitoring for signs of addiction, abuse, and misuse.
- Abuse or misuse of OPANA® ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the oxymorphone and can result in overdose and death.
- Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OPANA® ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Life-threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as

recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid- induced respiratory depression can exacerbate the sedating effects of opioids.

- While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OPANA® ER, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression especially within 24-72 hours of initiating therapy with and following dose increases of OPANA® ER.
- To reduce the risk of respiratory depression, proper dosing and titration of OPANA® ER are essential. Overestimating the OPANA® ER dosage when converting patients from another opioid product can result in fatal overdose with the first dose.
- Accidental ingestion of even one dose of OPANA ER, especially by children, can result in respiratory depression and death due to an overdose of oxymorphone.

Neonatal Opioid Withdrawal Syndrome

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

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

- Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on OPANA® ER therapy. The co-ingestion of alcohol with OPANA® ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.
- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of OPANA® ER with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics.
- If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.
- Advise both patients and caregivers about the risks of respiratory depression and sedation when OPANA® ER is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs.

Life-threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, and Debilitated Patients

The use of OPANA® ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: OPANA® ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of OPANA® ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients, because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating OPANA® ER and when OPANA® ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions

Potentially life-threatening hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients treated with OPANA® ER in the postmarket setting. The most commonly described clinical features in these reports were swelling of the face, eyes, mouth, lips, tongue, hands, and/or throat; dyspnea; hives, pruritus, and/or rash; and nausea/vomiting. If anaphylaxis or other hypersensitivity occurs, stop administration of OPANA® ER immediately, discontinue OPANA® ER permanently, and do not rechallenge with any formulation of oxymorphone. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried, as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Use in Patients with Hepatic Impairment

A study of OPANA® ER in patients with hepatic disease indicated greater plasma concentrations than those with normal hepatic function. OPANA® ER is contraindicated in patients with moderate or severe hepatic impairment. In patients with mild hepatic impairment, reduce the starting dose to the lowest dose and monitor for signs of respiratory and central nervous system depression.

Severe Hypotension

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

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

Consciousness

- In patients who may be susceptible to the intracranial effects of CO2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), OPANA® ER may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with OPANA® ER.
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of OPANA® ER in patients with impaired consciousness or coma.

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

- There have been post-marketing reports of difficulty in swallowing OPANA® ER tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick or otherwise wet OPANA® ER tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth.
- There have been rare post-marketing reports of cases of intestinal obstruction, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders, such as esophageal cancer or colon cancer, with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen.

Risks of Use in Patients with Gastrointestinal Conditions

- OPANA® ER is contraindicated in patients with known or suspected gastrointestinal obstructions, including paralytic ileus.
- The oxymorphone in OPANA® ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Increased Risk of Seizures in Patients with Seizure Disorders

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

Withdrawal

- Avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including OPANA® ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.
- When discontinuing OPANA® ER, gradually taper the dosage. Do not abruptly discontinue OPANA® ER.

Risks of Driving and Operating Machinery

OPANA® ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of OPANA® ER and know how they will react to the medication.

ADVERSE REACTIONS

Clinical Trial Experience

- The most common serious adverse events reported in clinical trials with administration of oxymorphone hydrochloride extended-release tablets were chest pain, pneumonia and vomiting.
- Adverse reactions reported at (≥2%) in placebo-controlled trials were: nausea (33%), constipation (28%), dizziness (18%), somnolence (17%), vomiting (16%), pruritus (15%), headache (12%), sweating increased (9%), dry mouth (6%), sedation (6%), diarrhea (4%), insomnia (4%), fatigue (4%), appetite decreased (3%), and abdominal pain (3%).
- In clinical trials 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.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

- OPANA® ER contains oxymorphone, a Schedule II controlled substance.
- The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

Abuse

- OPANA® ER contains oxymorphone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and tapentadol. OPANA® ER can be abused and is subject to misuse, addiction, and criminal diversion.
- 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.
- OPANA® ER, like other opioids, can be diverted for non-medical use into illicit channels of distribution.
- Careful record keeping of prescribing information, including quantity, frequency, and renewal requests as required by state law, is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to reduce abuse of opioid drugs.

Risks Specific to Abuse of OPANA® ER

- OPANA® ER is for oral use only. Abuse of OPANA® ER poses a risk of overdose and death. This risk is increased with concurrent abuse of OPANA® ER with alcohol and other substances. Taking cut, broken, chewed, crushed, or dissolved OPANA® ER enhances drug release and increases the risk of overdose and death.
- With parenteral abuse, cases of thrombotic microangiopathy (a condition characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia) have been reported; many cases resulted in hospitalization and treatment with plasmapheresis. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Dependence

- Both tolerance and physical dependence can develop during chronic opioid therapy.
- Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.
- OPANA® ER should not be abruptly discontinued. If OPANA® ER is abruptly discontinued in a physically dependent patient, a withdrawal syndrome may occur.
- Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs.

Please see accompanying full Prescribing Information, including Boxed WARNING and Medication Guide.

About Endo International plc
Endo International plc (NASDAQ / TSX: ENDP) is a highly focused generics and specialty branded pharmaceutical company delivering quality medicines to patients in need through excellence in development, manufacturing and commercialization. Endo has global headquarters in Dublin, Ireland, and U.S. headquarters in Malvern, PA. Learn more at www.endo.com.

Cautionary Note Regarding Forward-Looking Statements
This press release contains "forward-looking statements" including, but not limited to, the statements by Dr. Davis. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results could vary materially from Endo's expectations and projections. Risks and uncertainties include, among other things, general industry and market conditions; technological advances and patents attained by competitors; challenges inherent in the research and development and regulatory processes, including regulatory decisions; challenges related to product marketing, such as the unpredictability of market acceptance for new products and/or the acceptance of new indications for such products; inconsistency of treatment results among patients; potential difficulties in manufacturing; the outcome of litigation, settlement discussions or other adverse proceedings; general economic conditions; and governmental laws and regulations affecting domestic and foreign operations. Endo expressly disclaims any intent or obligation to update these forward-looking statements except as required by law. Additional information concerning these and other risk factors can be found in Endo's periodic reports filed with the U.S. Securities and Exchange Commission and in Canada on the System for Electronic Data Analysis and Retrieval ("SEDAR"), including current reports on Form 8-K, quarterly reports on Form 10-Q and annual reports on Form 10-K. Additional information about Endo is available on the World Wide Web at www.endo.com or you can contact the Endo Investor Relations department by calling (484) 216-0000.

To view the original version on PR Newswire, visit:http://www.prnewswire.com/news-releases/endo-statement-on-fda-advisory-committees-vote-related-to-opana-er-300423788.html

SOURCE Endo International plc

Endo International plc: Investors/Media: Stephen Mock,(845) 364-4833; Investors: Nina Goworek,(484) 216-6657; Media: Heather Zoumas-Lubeski, (484) 216-6829