Nearing Completion of its Fourth and Final Post-Marketing Epidemiological Study, Purdue Provides Background on Studies and Timelines

Culmination of epidemiologic research represents years of collaboration with FDA, and experts in epidemiology and opioid abuse, in a new and evolving scientific field

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For more than eight years, Purdue Pharma L.P. has been diligently working on several post-marketing epidemiological studies with the U.S. Food & Drug Administration (FDA) and preeminent experts in the fields of substance abuse and epidemiology. These post-marketing requirement (PMR) studies, designed by Purdue Pharma L.P., in consultation with and agreed to by the FDA, are intended to assess the effects of reformulated OxyContin® (oxycodone HCl) extended-release tablets with abuse-deterrent properties (ADPs) on abuse, misuse, overdose, and death.

Opioids with ADP create barriers to physical and chemical manipulation for certain routes and types of abuse, such as resisting crushing or making it more difficult to crush before snorting and impeding preparation for intravenous injection or making it more difficult due to gelling properties. The FDA supports the development of opioids with ADPs as one potentially important step in helping deter prescription opioid abuse and misuse.[1]

It is important to note that opioids with ADPs will not stop all prescription opioid abuse, but they are one part of a comprehensive multi-stakeholder approach needed to address this complex public health issue. All opioids, including those with ADPs, expose users to the risks of addiction, abuse, and misuse which can lead to overdose and death.

In 2010, Purdue received FDA approval for reformulated OxyContin after spending nearly a decade and hundreds of millions of dollars on its development. In 2013, based on laboratory and clinical data, the FDA granted OxyContin the first-ever label stating that the medication has ADPs that are expected to make it more difficult to abuse via injection and snorting. However, abuse by injection, intranasal and oral route is still possible. Today, the FDA continues to encourage the development of opioid pain medications that are harder to manipulate and abuse.[1]

Since 2010 Purdue has had a regular dialogue with the FDA on the design and interpretation of these types of studies, and the company has provided the agency with study updates and data regularly on an agreed-upon timeline since 2012 following submission of the first PMR protocols.

PMR studies are conducted by a manufacturer after a regulatory approval to gather additional information about a product's safety, efficacy, or optimal use. PMR study protocols describe how the study will be conducted, including its methodology, design, data sources, study population, and outcomes. Additional information about PMR studies is available on the FDA's website.

As required by the FDA, Purdue submitted its first annual report with updates on the PMR studies in 2012 and the company continued to submit annual reports from 2014 to 2019. Over these years, the preferred data sources and analytical approaches evolved and, in 2016 the FDA issued final PMRs with the four studies described below. This extensive timeline reflects the complexity of the evolving science of ADPs and the evaluation of their effectiveness in reducing abuse.

The studies were designed using multiple real-world data sources and populations, including NAVIPPRO® system, RADARS® System Poison Center Program, RADARS® System Treatment Center Programs Combined, and commercial and Medicaid claims data. An overview of each study and timing for when its protocols were finalized and data were or will be submitted to the FDA follows:

Study	Description	Protocols Finalized	Study Report Submitted to FDA
Study 1	Evaluated changes in opioid abuse in a sentinel population of adults assessed for substance use disorder and treatment planning at substance abuse treatment centers using the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) System	June 2017	July 2018
Study 2	Evaluated changes in opioid intentional exposures from reports to US poison control centers nationally, in the Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program	June 2017	July 2018
Study 3	Evaluated changes in opioid abuse in a sentinel population of adults entering RADARS® System substance abuse treatment centers	June 2017	April 2019
Study 4	Evaluated fatal and non-fatal opioid overdose among a population of patients prescribed OxyContin using commercial and Medicaid claims data	September 2018	To be submitted: August 2019

Purdue looks forward to completing and submitting the final study and discussing the results of the program in its entirety with the FDA. As agreed to with the FDA, Purdue will share study reports with the agency for their review and analysis prior to disseminating the data to the scientific community.

Each study provides meaningful standalone results, and are most informative when interpreted together considering the totality of evidence to assess the effect of the reformulation of OxyContin using a mosaic of studies and supportive information.

Purdue is committed to addressing the opioid addiction crisis and has taken numerous actions to stem prescription opioid abuse in close collaboration with states, communities, industry partners, and law enforcement agencies. For additional information about Purdue's commitment to addressing the opioid crisis, please read more about what we're doing now.

Abbreviations:
NAVIPPRO®: National Addictions Vigilance Intervention and Prevention Program
RADARS®: Researched Abuse, Diversion and Addiction-Related Surveillance

Reference:
1. U.S. Food and Drug Administration. Abuse-Deterrent Opioid Analgesics. 2018. Accessed June 5, 2019. Retrieved from https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/abuse-deterrent-opioid-analgesics.

Please read the OxyContin Full Prescribing Information, including Box Warning and additional Important Safety Information as follows.

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

OXYCONTIN® 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 OXYCONTIN and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)].*

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products *[see Warnings and Precautions (5.2)].* Under the requirements of REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of OXYCONTIN. Monitor for respiratory depression, especially during initiation of OXYCONTIN or following a dose increase. Instruct patients to swallow OXYCONTIN tablets whole; crushing, chewing, or dissolving OXYCONTIN tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone *[see Warnings and Precautions (5.3)]*.

Accidental Ingestion

Accidental ingestion of even one dose of OXYCONTIN, especially by children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.3)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.4)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of OXYCONTIN with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving OXYCONTIN and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.5), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

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 *[see Warnings and Precautions (5.6), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of OXYCONTIN 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.**

Adult Indications and Usage

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

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations *[see Warnings and Precautions (5)]*, reserve OxyContin 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.
- OxyContin is not indicated as an as-needed (prn) analgesic.

IMPORTANT SAFETY INFORMATION

Contraindications

OxyContin is contraindicated in patients with:

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

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse

- OxyContin contains oxycodone, a Schedule II controlled substance. OxyContin exposes users to the risks of opioid addiction, abuse, and misuse. Because extended-release products such as OxyContin deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.
- Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OxyContin. 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 OxyContin, and monitor all patients receiving OxyContin 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 the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as OxyContin, but use in such patients necessitates intensive counseling about the risks and proper use of OxyContin along with intensive monitoring for signs of addiction, abuse, and misuse.

- Abuse or misuse of OxyContin by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of oxycodone 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 OxyContin. 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.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

- To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:
  - complete a REMS-compliant education program,
  - counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
  - emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
  - consider other tools to improve patient, household, and community safety.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at http://www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended, and if not immediately recognized and treated, may lead to respiratory arrest and death.
- While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OxyContin, the risk is greatest during the initiation of therapy or following a dosage increase. Closely monitor patients for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of OxyContin.
- To reduce the risk of respiratory depression, proper dosing and titration of OxyContin are essential. Overestimating the OxyContin dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.
- Accidental ingestion of even one dose of OxyContin, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of OxyContin 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 syndrome 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 of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use with a CYP3A4 inhibitor, such as macrolide antibiotics, azole-antifungal agents, and protease inhibitors, particularly when an inhibitor is added after a stable dose of OxyContin is achieved, and discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression. Monitor patients closely at frequent intervals and consider dosage reduction of OxyContin until stable drug effects are achieved. Concomitant use of OxyContin with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. Monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of OxyContin with benzodiazepines or CNS depressants (e.g., non-benzodiazepines sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- 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 OxyContin 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.

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

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in 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 OxyContin and when OxyContin is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. 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.

Severe Hypotension

- OxyContin 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 after concurrent administration of certain CNS depressants drugs (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of OxyContin. In patients with circulatory shock, OxyContin may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of OxyContin 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 CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), OxyContin may reduce respiratory drive, and the resultant

CO_2 retention can further increase intracranial pressure. Monitor those patients for signs of sedation and respiratory depression, particularly when initiating therapy with OxyContin. Opioids may obscure the clinical course in a patient with a head injury. Avoid the use of OxyContin 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 swallowing OxyContin tablets. These reports include choking, gagging, regurgitation, and tablets stuck in the throat. Instruct patients not to pre-soak, lick or otherwise wet OxyContin 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, and exacerbations of diverticulitis, 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

- OxyContin is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The oxycodone in OxyContin 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.

Increased Risk of Seizures in Patients with Seizure Disorders

- The oxycodone in OxyContin may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during OxyContin therapy.

Withdrawal

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

Risks of Driving and Operating Machinery

- OxyContin 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 OxyContin and know how they will react to the medication.

Laboratory Monitoring

- Not every urine drug test for “opioids” or “opiates” detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified “cut-off” value as “negative.” Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results.

ADVERSE REACTIONS

- OxyContin may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock.
- The most common adverse reactions (> 5%) reported by adult patients in clinical trials comparing OxyContin with placebo are constipation, nausea, somnolence, dizziness, pruritus, vomiting, headache, dry mouth, asthenia, and sweating.

To report SUSPECTED ADVERSE REACTIONS, contact Purdue Pharma L.P. at 1-888-726-7535, option 2, or FDA at 1-800-FDA-1088.

Please read the Full Prescribing Information including Boxed Warning.