Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	March 17, 2025
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Product Name:	Opana (oxymorphone hydrochloride immediate-release)
Pediatric Labeling Approval Date:	October 25, 2019
Application Type/Number:	NDA 021611
Applicant:	Endo Pharmaceuticals, Inc.
TTT Record ID:	2024-12089

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Opana (oxymorphone hydrochloride) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with oxymorphone hydrochloride (hereafter refer to as "oxymorphone") in pediatric patients.

Oxymorphone, an opioid agonist, was initially approved by FDA on April 2, 1959, as an injectable formulation. Oxymorphone is currently available as oral tablets indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Oxymorphone is not approved for a pediatric indication.

This pediatric postmarketing safety review was stimulated by pediatric labeling on October 25, 2019, that described pediatric studies that failed to establish safety and effectiveness for oxymorphone immediate-release tablets. An additional pediatric labeling change for oxymorphone extended-release (ER) on April 28, 2022, described pediatric studies that were inconclusive to establish safety and effectiveness for chronic use of oxymorphone ER tablets. A pediatric safety review for Opana has not previously been presented to the Pediatric Advisory Committee.

DPV searched FAERS for all U.S. serious reports with oxymorphone in pediatric patients less than 18 years of age through December 12, 2024, and identified 224 reports; however, all reports were excluded from further discussion because they: represented duplicate entries in the FAERS system; did not describe an exposure to oxymorphone; did not refer to a pediatric patient; described transplacental exposures; did not contain sufficient information to assess causality; or described already-labeled adverse events, such as oxymorphone misuse/abuse.

DPV did not identify any new pediatric safety concerns for oxymorphone at this time and will continue routine pharmacovigilance monitoring for oxymorphone.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Opana (oxymorphone hydrochloride) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with oxymorphone hydrochloride (hereafter refer to as "oxymorphone") in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Oxymorphone, an opioid agonist, was initially approved by FDA on April 2, 1959, as an injectable formulation.[1] Oxymorphone is currently available as oral tablets indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Oxymorphone is not approved for a pediatric indication.

Regulatory history relevant to this review is highlighted below.

- June 22, 2006 – FDA approved oxymorphone immediate-release (IR) (Opana, NDA 021611) and extended-release (ER) oral tablets (Opana ER, NDA 021610) for the relief of moderate to severe acute pain where the use of an opioid is appropriate.[2,3]

- June 14, 2010 – FDA approved generic oxymorphone ER tablets (reference label drug NDA 021610).[4]

- September 27, 2010 – FDA approved generic oxymorphone IR tablets (reference label drug NDA 021611).[4]

- December 9, 2011 – FDA approved a new formulation of oxymorphone ER under NDA 201655 (hereafter refer to as "reformulated oxymorphone ER") 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. The Applicant, Endo Pharmaceuticals, replaced the original formulation with reformulated oxymorphone ER.[5]

- October 25, 2019 – pediatric labeling change for oxymorphone IR (NDA 021611) described pediatric studies that failed to establish safety and effectiveness for oxymorphone IR tablets.[2]

- June 15, 2020 – oxymorphone IR (NDA 021611) was withdrawn from marketing.[6]

- December 23, 2020 – reformulated oxymorphone ER (NDA 201655) was withdrawn from marketing.[7]

- April 28, 2022 – pediatric labeling change for oxymorphone ER (NDA 021610) described pediatric studies that were inconclusive to establish safety and effectiveness for chronic use of oxymorphone ER tablets. Additionally, limited data from one study suggested oxymorphone ER tablets are not recommended for post-surgical pain in pediatric patients.[3]

This pediatric postmarketing safety review was stimulated by pediatric labeling on October 25, 2019, for oxymorphone IR. A pediatric safety review for Opana has not previously been presented to the Pediatric Advisory Committee.[8]

1.2 RELEVANT LABELED SAFETY INFORMATION

Oxymorphone labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional oxymorphone labeling information, please refer to the full prescribing information.[9,10]

	Oxymorphone IR[9]	Oxymorphone ER[10]
BOXED WARNINGS	**WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS** ***See full prescribing information for complete boxed warning.*** • **Oxymorphone Hydrochloride Tablets exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patients risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)** • **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.2)** • **Accidental ingestion of Oxymorphone Hydrochloride Tablets, especially by children, can result in a fatal overdose of oxymorphone. (5.2)** • **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 for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.3,7)** • **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. (5.5)** • **Prolonged use of Oxymorphone Hydrochloride Tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5. 4)** • **Instruct patients not to consume alcohol or any product containing alcohol while taking Oxymorphone Hydrochloride Tablets because co-ingestion can result in fatal plasma oxymorphone levels. (5.3)**	**WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF OXYMORPHONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS** ***See full prescribing information for complete boxed warning.*** • **Oxymorphone Hydrochloride Extended-Release Tablets expose users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing, and monitor regularly these behaviors and conditions. (5.1)** • **Serious life-threatening or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow Oxymorphone Hydrochloride Extended-Release Tablets whole to avoid exposure to a potentially fatal dose of oxymorphone. (5.2)** • **Accidental ingestion of Oxymorphone Hydrochloride Extended-Release Tablets, especially by children, can result in fatal overdose of oxymorphone. (5.2)** • **Instruct patients not to consume alcohol or any product containing alcohol while taking Oxymorphone Hydrochloride Extended-Release Tablets because co-ingestion can result in fatal plasma oxymorphone levels. (5.3)** • **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 for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.3, 7)** • **Prolonged use of Oxymorphone Hydrochloride Extended-Release Tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. 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. (5.4)** • **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. (5.5)**

	Oxymorphone IR[9]	Oxymorphone ER[10]
CONTRAINDICATIONS	• Significant respiratory depression. (4) • Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4) • Known or suspected gastrointestinal obstruction, including paralytic ileus. (4) • Known hypersensitivity to oxymorphone, any other ingredients in Oxymorphone Hydrochloride Tablets(4) • Moderate or severe hepatic impairment (4)	• Significant respiratory depression (4) • Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment (4) • Hypersensitivity to oxymorphone (4) • Moderate or severe hepatic impairment (4) • Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
WARNINGS AND PRECAUTIONS	• Opioid Induced Hyperalgesia (OIH) and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (5.6). • Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Regularly evaluate, particularly during initiation and titration. (5.7) • Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions: If symptoms occur, stop administration immediately, discontinue permanently, and do not rechallenge with any oxymorphone formulation. (5.8) • Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.9) • Severe Hypotension: Regularly evaluate during dosage initiation and titration. Avoid use of Oxymorphone Hydrochloride Tablets in patients with circulatory shock. (5.10) • Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Regularly evaluate for sedation and respiratory depression. Avoid use of Oxymorphone Hydrochloride Tablets in patients with impaired consciousness or coma. (5.11) (5)	• Opioid-Induced Hyperalgesia and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation. (5.6) • Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly Cachectic or Debilitated Patients: Regularly evaluate closely particularly during initiation and titration. (5.7) • Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions: If symptoms occur, stop administration immediately, discontinue permanently, and do not rechallenge with any other oxymorphone formulation. (5.8) • Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.9) • Severe Hypotension: Regularly evaluate during dose initiation and titration. Avoid use of oxymorphone hydrochloride extended-release tablets in patients with circulatory shock. (5.11) • Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of Oxymorphone Hydrochloride Extended-Release Tablets in patients with impaired consciousness or coma. (5.12)

	Oxymorphone IR[9]	Oxymorphone ER[10]
ADVERSE REACTIONS	Adverse reactions (≥ 2% of patients): Nausea, pyrexia, somnolence, vomiting, pruritus, headache, dizziness, constipation, and confusion. (6.1)	Adverse reactions in ≥2% of patients in placebo-controlled trials: nausea, constipation, dizziness, somnolence, vomiting, pruritus, headache, sweating increased, dry mouth, sedation, diarrhea, insomnia, fatigue, appetite decreased, and abdominal pain. (6.1)
DRUG INTERACTIONS	• Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue Oxymorphone Hydrochloride Tablets if serotonin syndrome is suspected. (7) • Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with Oxymorphone Hydrochloride Tablets because they may reduce analgesic effect of Oxymorphone Hydrochloride Tablets or precipitate withdrawal symptoms. (7) • Monoamine oxidase inhibitors (MAOIs): Can potentiate the effects of oxymorphone. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping such treatment with an MAOI. (7)	• Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue Oxymorphone Hydrochloride Extended-Release Tablets if serotonin syndrome is suspected. (7) • Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with Oxymorphone Hydrochloride Extended-Release Tablets because they may reduce analgesic effect of Oxymorphone Hydrochloride Extended-Release Tablets or precipitate withdrawal symptoms. (7) • Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of oxymorphone. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI. (7)
8.4 Pediatric Use	Safety and effectiveness for pediatric patients, 0 to 17 years, have not been established. An open-label study was conducted in 58 pediatric patients 12 years of age and older with postoperative pain using Oxymorphone Hydrochloride Tablets. Efficacy was not demonstrated in this population treated with doses expected to be comparable to effective starting doses in adults. In addition, pharmacokinetic results demonstrated that treatment with Oxymorphone Hydrochloride Tablets resulted in substantially higher systemic exposures to oxymorphone in 2 out of 24 patients. Oxymorphone Hydrochloride Tablets are not recommended for use in the pediatric population.	The safety and effectiveness of Oxymorphone Hydrochloride Extended-Release Tablets in patients below the age of 18 years have not been established. Two open-label studies were conducted in a total of 42 pediatric patients between the ages of 7 to 17 years requiring continuous, around the clock opioid treatment. The available safety and efficacy data were inconclusive for chronic use of Oxymorphone Hydrochloride Extended-Release Tablets. Limited data from one of the studies suggested that Oxymorphone Hydrochloride Extended-Release Tablets is not recommended for post-surgical pain.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	December 13, 2024
Time period of search	All reports through December 12, 2024
Search type	RxLogix Pediatric Focused Review Alert - DPV
Product terms	Product Active Ingredient: Oxymorphone
MedDRA search terms (Version 27.1)	All Preferred Terms
Other search terms†	Case Seriousness: Serious

* See Appendix A for a description of the FAERS database.
†For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities

3 RESULTS

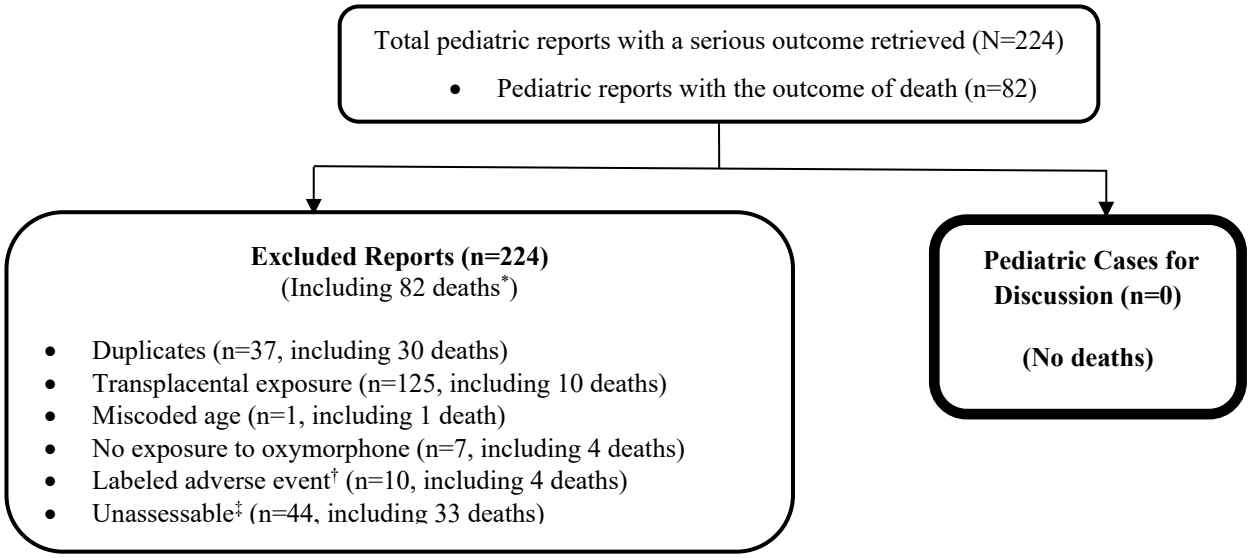
3.1 FAERS

3.1.1 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 224[a] U.S. serious pediatric reports for patients less than 18 years old through December 12, 2024. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 224 reports from the case series for the reasons listed in Figure 1.

[a] Includes 15 pediatric reports that were identified among reports not coded with an age.

Figure 1. Selection of U.S. Serious Pediatric Cases With Oxymorphone



* Eighty-two excluded U.S. FAERS reports with a serious outcome described fatal outcomes. After accounting for duplicate reports (n=30), we identified 52 unique cases describing fatal outcomes. These reports were excluded for the following reasons: 10 cases reported fetal or neonatal death following transplacental exposure of multiple opioids; these cases did not contain sufficient clinical details to determine the extent to which oxymorphone contributed to the fatal outcome. One case described death in an adult patient who was miscoded as a pediatric patient who died from a "toxicity to various agents." Four cases described death in patients who had no exposure to oxymorphone products. Four cases described adolescent patients who died from accidental oxymorphone overdose following oxymorphone abuse or misuse (labeled adverse event). Thirty-three cases described patients who died following polysubstance exposures; these cases did not provide sufficient information to determine the extent to which oxymorphone contributed to the fatal outcome.

† Labeled adverse events do not represent increased severity.

‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course, and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.3 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV searched FAERS for all U.S. serious reports with oxymorphone in pediatric patients less than 18 years of age through December 12, 2024, and identified 224 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no unexpected deaths directly associated with oxymorphone in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for oxymorphone at this time and will continue routine pharmacovigilance monitoring for oxymorphone.

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7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.