

Pediatric Focused Safety Review
**OxyContin (oxycodone hydrochloride
extended-release)**
Pediatric Advisory Committee Meeting
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Outline

- **Background Information**
- Pediatric Studies
- Safety
- Summary

Background Drug Information

- **Drug:** OxyContin (oxycodone hydrochloride (HCl) extended-release)
- **Original FDA Approval Date:** December 12, 1995
 - Reformulated: April 5, 2010
 - Approval in pediatric population: August 13, 2015
- **Therapeutic Category:** Opioid agonist
- **Pediatric Indication:** Opioid-tolerant pediatric patients 11 years and older already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent for at least two days immediately preceding dosing with OxyContin
 - Adult indication: management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
- **Formulation:** Oral tablets
 - 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
- **Sponsor:** Purdue Pharma L.P.

OxyContin Authorized Generics

- An authorized generic is a brand-name drug (may have different markings or color) marketed by subsidiaries of the brand or third parties under synonymous names
- Oxycodone HCl extended-release
 - Approved August 14, 2014
 - Supplied in all of the same strengths as OxyContin (10 mg, 15 mg, 20 mg, 30 mg, 40mg, 60 mg, and 80 mg)

Background Drug Information

Boxed Warning

WARNING: ADDICTION, ABUSE AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and CYTOCHROME P450 3A4 INTERACTION

See full prescribing information for complete boxed warning.

- **OXYCONTIN exposes users to risks of addictions, abuse and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and monitor regularly for development of 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 OXYCONTIN tablets whole to avoid exposure to a potentially fatal dose of oxycodone. (5.2)**
- **Accidental ingestion of OXYCONTIN, especially in children, can result in a fatal overdose of oxycodone. (5.2)**
- **Prolonged use of OXYCONTIN 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. (5.3)**
- **Initiation of CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone from OXYCONTIN. (5.14)**

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Pediatric Studies: Safety

OxyContin (oxycodone HCl extended-release)

- Open-label study in 155 patients ages 6 to <17 years
 - Lack of safety data in patients less than 11 years of age
 - Previously receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent on the two days immediately preceding dosing with OxyContin
 - Initiated on a total daily dose ranging between 20 mg and 100 mg depending on prior opioid dose
- Safety results
 - Vomiting, nausea, headache, pyrexia, and constipation

Postmarketing Requirement (PMR)

- Two PMRs issued at the time of the expansion of the OxyContin approval to the pediatric population
 - PMR 2923-1 Enhanced pharmacovigilance
 - PMR 2923-2 Drug utilization study

Enhanced Pharmacovigilance PMR

OxyContin (oxycodone HCl extended-release)

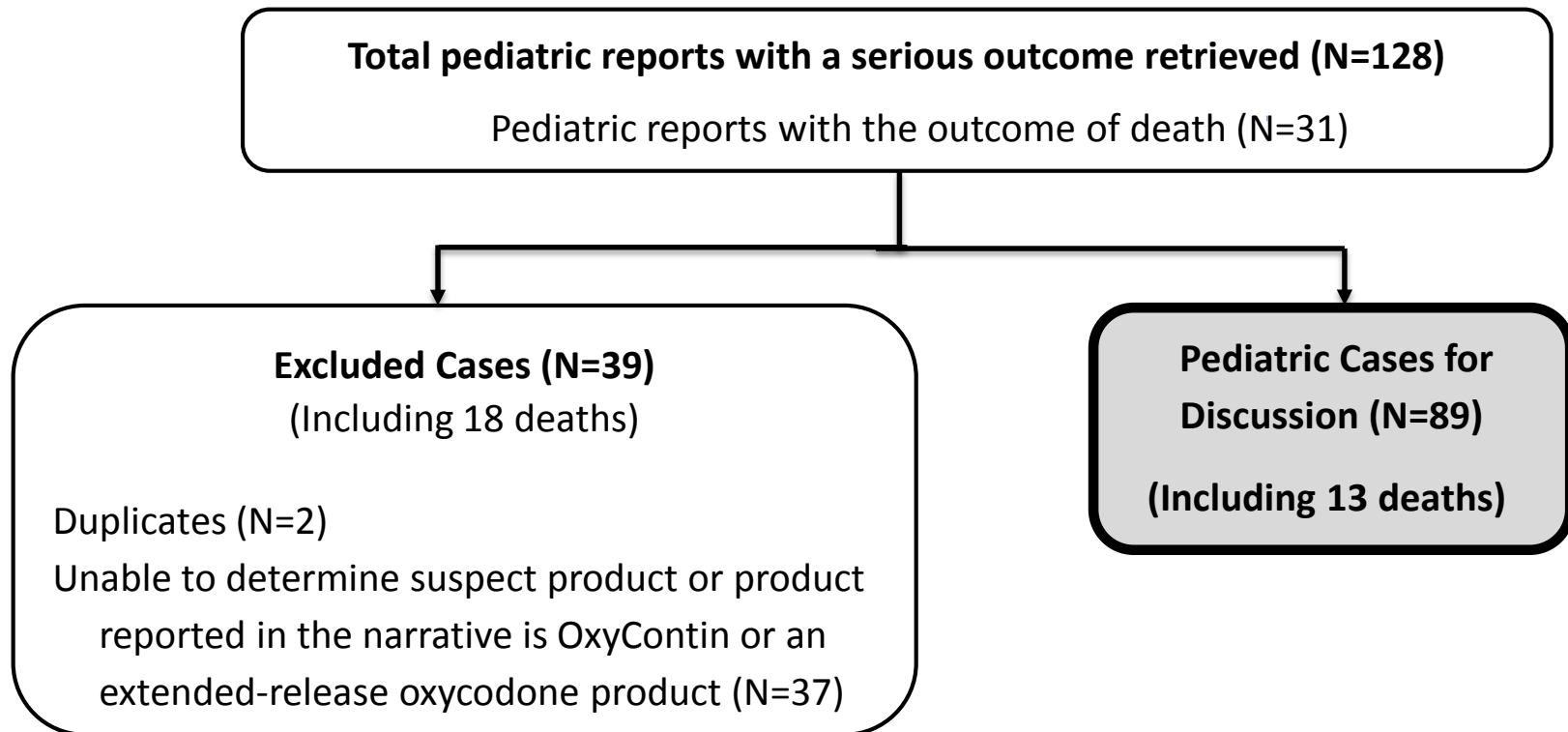
- Analyze postmarketing spontaneous adverse events in children <17 years of age:
 - Adverse events of interest: respiratory depression, accidental injury, overdose, misuse, accidental exposure, and medication errors (included off label uses)
 - Reporting period: August 13, 2015* through October 12, 2018
 - Final comprehensive analysis under evaluation by the FDA

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FAERS Pediatric Case Selection

Serious* U.S. Pediatric Cases for OxyContin Initially Received by the FDA, August 13, 2015 to December 31, 2018



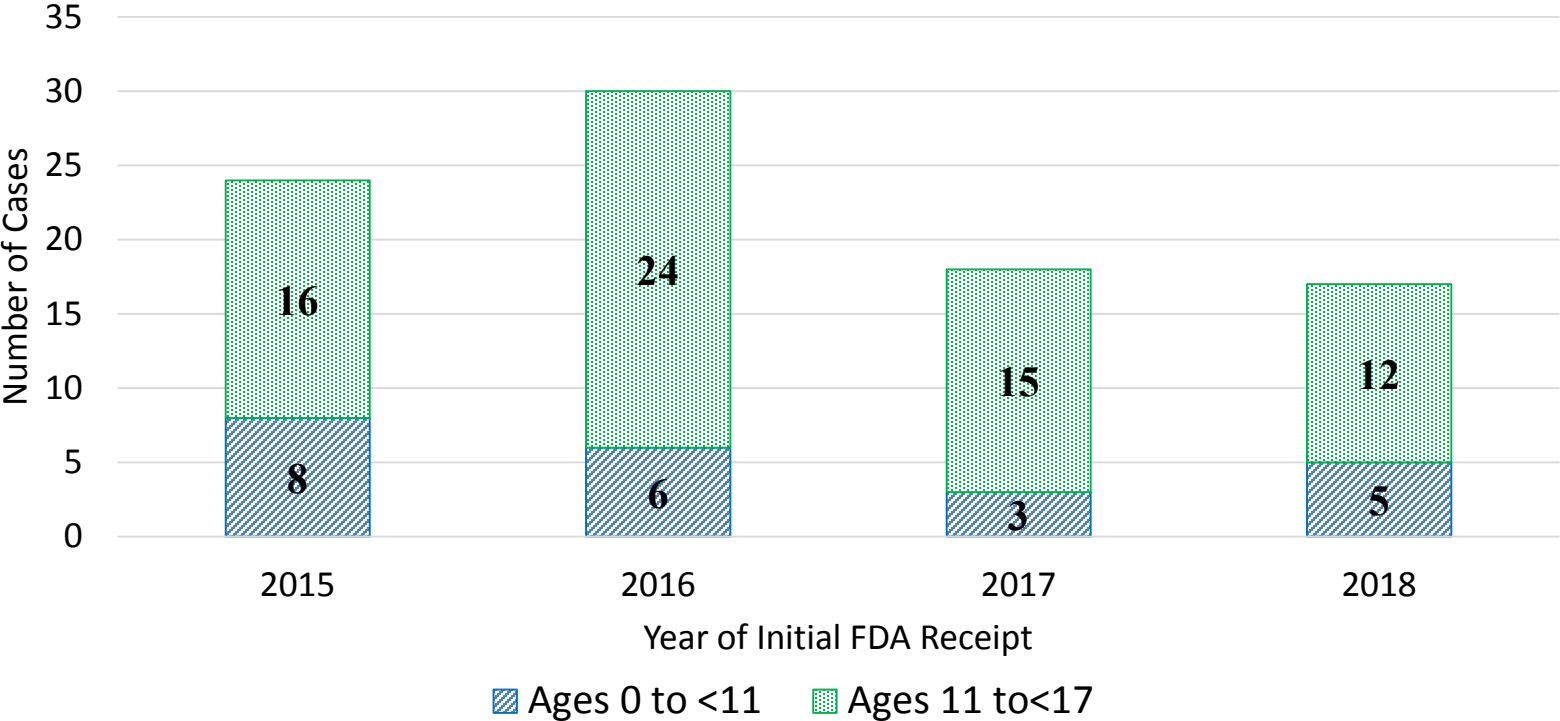
FAERS = FDA's Adverse Event Reporting System

* As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events.



FAERS Cases by Year of FDA Receipt

Serious* U.S. Pediatric Cases for OxyContin From August 13, 2015† to December 31, 2018 (N=89)



* Regulatory definition of serious adverse event reporting as per 21 CFR 314.80

† Date of approval in pediatric population



Case Demographics and Case Source

Serious* U.S. Pediatric Cases for OxyContin Initially Received by the FDA August 13, 2015 to December 31, 2018

	Ages 11 to <17 (N=67)	Ages 0 to <11 (N=22)
Age		
0 - < 1 month	0	5 [†]
1 month - <2 years	0	6
2 - < 6 years	0	8
6 - <12 years	1	3
12 - < 17 years	66	0
Sex		
Male	28	16
Female	36	4
Unknown	3	2
Reported Source of Case Report		
News media	61	11
Postmarketing study report	4	7
Literature	1	0
Lawyer	1	3
Via another pharmaceutical company	0	1

Representative FAERS Case From the News Media

- A 16-year-old female began taking OxyContin that was prescribed to her mother. According to the article, the patient became addicted and later started using heroin.

Reported adverse events are underlined: Drug abuse and drug addiction



Frequently Reported Adverse Events:^{*}

11 to <17 Years (N=67)

Serious[†] U.S. Pediatric Cases for OxyContin Initially Received by the FDA August 13, 2015 to December 31, 2018

- Drug abuse (N=43)
- Drug dependence (N=36)
- Drug overdose (N=11)
- Malaise (N=5)
- Somnolence (N=4)



Frequently Reported Adverse Events:^{*}

0 to <11 Years (N=22)

Serious[†] U.S. Pediatric Cases for OxyContin Initially Received by the FDA August 13, 2015 to December 31, 2018

- Accidental exposures (N=7)
 - Somnolence (N=3)
 - Decreased respiratory rate/ abnormal breathing (N=2)
 - Lethargic (N=1) and pallor (N=1)
 - No adverse event (N=2) and adverse event not reported (N=1)
- Drug overdose (N=6)[‡]
- Neonatal opioid withdrawal syndrome (NOWS) (N=4)

* A case may report more than one adverse event

† Regulatory definition of serious adverse event reporting as per 21 CFR 314.80

‡ Not otherwise reported as an accidental exposure



Reported Serious* Outcomes

Serious* U.S. Pediatric Cases for OxyContin Initially Received by the FDA August 13, 2015 to December 31, 2018

	Ages 11 to <17 (N=67)	Ages 0 to <11 (N=22)
Serious Outcome*		
Death	4	9
Life-threatening	4	1
Hospitalization	3	1
Disability	1	0
Congenital anomaly	0	1
Other serious	66	18

* Cases may have more than one outcome. As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events.



Evaluation of Prescribed Use

Serious* U.S. Pediatric Cases for OxyContin Initially Received by the FDA August 13, 2015 to December 31, 2018

	Ages 11 to <17 (N=67)	Ages 0 to <11 (N=22)
Reported as Prescribed Use		
Yes[†]	7	1
Suspected to be prescribed/No/Not specified	60	21
<u>Suspected to be prescribed[‡]</u>	<u>5</u>	<u>0</u>
<u>Not prescribed</u>	<u>21</u>	<u>3</u>
Taken from a family member or residence	6	0
Given to by a family member, friend, coach, etc.	10	3
Mentioned not prescribed	5	0
<u>Not specified/other</u>	<u>34</u>	<u>18</u>
Accidental exposure	0	7
Transplacental exposure	0	5
Unknown	34	6

† All eight cases of prescribed use lacked information to assess opioid tolerance.

‡ Five cases did not explicitly state OxyContin use was prescribed; however, it was likely prescribed for the pain specified in the case (back surgery, nephrolithiasis, migraine pain, knee pain, and unspecified, non-cancer pain)

Evaluation of the Reason for Use

Serious* U.S. Pediatric Cases for OxyContin Initially Received by the FDA August 13, 2015 to December 31, 2018

	Ages 11 to <17 (N=67)	Ages 0 to <11 (N=22)
Reported Reason for Use		
Pain, cancer-related	1	1
Pain, non-cancer related/ unspecified pain	11	0
<i>Post-operative pain (back, hernia, knee)</i>	3	0
<i>Nephrolithiasis</i>	2	0
<i>Shoulder pain</i>	2	0
<i>Knee pain</i>	1	0
<i>Migraine</i>	1	0
<i>Unspecified pain</i>	2	0
Other	43	17
<i>Drug abuse/misuse</i>	40	1
<i>Intentional overdose</i>	3	0
<i>Accidental exposure</i>	0	7
<i>Intentional administration to a child</i>	0	4
<i>Transplacental exposure</i>	0	5
Unknown	12	4

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Summary: Pediatric Safety Review

- Only ~10% (8/89) of the cases, primarily in the ages 11 to <17 years, mentioned prescribed OxyContin use
 - Opioid tolerance status unassessable
- The majority of the 13 cases with an outcome of death describe the death in the context of drug abuse, drug overdose, or accidental exposure
- The most frequently reported adverse events
 - Ages 11 to <17 years - drug addiction and drug abuse
 - Ages 0 to <11 years – drug overdose and accidental exposures
 - This finding underscores the need for continued education around environmental safety with opioid products

Summary: Pediatric Safety Review

- No new safety signals were identified from our safety review *or* enhanced pharmacovigilance PMR interim reports
- Based on the data, FDA recommends to continue ongoing monitoring of postmarketing safety reports and completion of the PMRs

