FDA Briefing Document

Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Pediatric (PAC) Advisory Committee

Thursday, September 26, 2019

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the pediatric-focused safety review for OxyContin (oxycodone hydrochloride) extended-release tablets, as mandated by the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144), and pediatric data considerations for opioid analgesics labeling and Pediatric Research Equity Act studies for opioids generally, using Opana IR as an example, to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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OFFICE DIRECTOR MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Office of Surveillance and Epidemiology (OSE)

Date:	August 27, 2019
From:	Judy Staffa, Ph.D., R.Ph. Associate Director for Public Health Initiatives Office of Surveillance and Epidemiology, CDER, FDA
To:	Chair, Members and Invited Guests Pediatric Advisory Committee (PAC) Drug Safety and Risk Management Advisory Committee (DSaRM)
Subject:	Overview of the September 26, 2019 PAC/DSaRM meeting

I. Background

FDA is convening this meeting of the Pediatric Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the pediatric-focused safety review for OxyContin (oxycodone hydrochloride) extended-release tablets, as mandated by the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144), and to discuss pediatric data considerations for opioid analgesics labeling and Pediatric Research Equity Act studies for opioids generally, using Opana IR (immediate-release oxymorphone) as an example.

II. Issues for consideration

Prior to our discussion of these two topics, we provide a context for understanding the clinical need and associated risks of opioid analgesic therapy in children. Our guest speaker from the American Academy of Pediatrics will provide a clinical perspective on the need for opioid analgesic therapy in pediatric care, and our background document includes a review from Dr. Ibrahim in the Division of Epidemiology II in which actual patterns of opioid analgesic use in children are examined overall, and for different opioid moieties, using proprietary data available to the Agency.

For all regulatory questions involving opioids, FDA considers the potential broader public health implications, including potential harms associated with misuse and abuse of the drugs by patients or others in the community. To inform this consideration and discussion, the review included from Dr. Greene in the Division of Epidemiology II provides recent data on prescription drug misuse and abuse in pediatric populations, as well as a review of the epidemiologic literature

examining opioid analgesic misuse, abuse, addiction and overdose in children and adolescents, and the risk of these adverse outcomes following opioid analgesic therapy in these populations.

Our first discussion topic is our mandated safety review of OxyContin, subsequent to its 2015 approval for use in opioid-tolerant pediatric patients 11 years of age and older, who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent. To support this discussion, we have included our routine safety review from the Division of Epidemiology II, which describes patterns of utilization of OxyContin among pediatric patients in the outpatient retail pharmacy setting, and our review from the Division of Pharmacovigilance II, which evaluates postmarketing adverse event reports with a serious outcome for OxyContin in pediatric patients. In both of these reviews, we also describe the goals and status of the postmarketing required studies (PMRs) that the OxyContin sponsor is completing, as they also relate to examining utilization and safety of the product in pediatric populations.

Our second discussion topic focuses more generally on the pediatric data collected during studies conducted by sponsors under the Pediatric Research Equity Act (PREA), and how best to use this information in product labeling to inform clinical use of these products. As an example, to illustrate the challenges we face, a description of pediatric studies conducted by the sponsor of Opana IR (immediate-release oxymorphone) and the sponsor's proposed pediatric labeling is included in a review by FDA's Office of Clinical Pharmacology and Division of Anesthesia, Analgesia and Addiction Products.

III. Draft Topics for Discussion

a. No new safety signals were identified for OxyContin (oxycodone hydrochloride) extended release tablets in the current pediatric safety review. FDA recommends continuing ongoing, routine, post-market safety monitoring, along with completion of the post-marketing required studies by the sponsor. Does the Committee agree?

b. Given the pain management needs for pediatric patients, including the need for approved labeling that describes the safe and effective use of opioid products in pediatrics as they are already being used clinically in that context, and given the public health considerations around opioid misuse and abuse, discuss appropriate strategies for describing the results of studies conducted under PREA in labeling.

c. Extrapolation of efficacy from adults to pediatric populations down to two years of age and older for opioid analgesics is typically permitted provided that pharmacokinetic (PK) data are submitted to demonstrate that the systemic exposures to the drug are similar between adults and this pediatric population. Discuss whether an opioid product should be labeled with a pediatric pain indication in situations where the PK data demonstrate comparable exposures to the drug between adults and children but where open-label data call in to question

the efficacy of the product in pediatric populations, such as the high frequency of discontinuations due to lack of efficacy that was seen with Opana IR in pediatrics.

d. With Opana IR, higher systemic exposures were observed in 2 of the 24 patients in the PK and safety study conducted in >12 to 17 years of age. Although these patients were excluded from the pharmacokinetic analysis and did not experience any serious safety issues in the context of the study, discuss the implications of outlier higher systemic exposures to study medication on the safety of an opioid product when used in a broader pediatric population.

e. Discuss if pediatric labeling should be approved for Opana IR (immediate-release oxymorphone) and, if so, how the pediatric information should be described in labeling.

As always, we are most appreciative of the time and energy invested by our Committees in providing us advice around challenging regulatory issues. We look forward to a fruitful discussion.

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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

M E M O R A N D U M

DATE: August 16, 2019

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TO: Chair, Members and Invited Guests
Pediatric Advisory Committee (PAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Approach to Pediatric Data for Opioid Analgesic Drug Products

1. Introduction

It is critically important that drug products be formally studied in relevant pediatric populations to establish their safety and effectiveness, given the potentially differing effects of drugs in and

needs of pediatric populations as compared to adults. In particular, pediatric pain management represents an unmet need in that there are a limited number of approved analgesic products that contain pediatric indications or labeling, including for opioid analgesics despite their long history of clinical use. Fortunately, the majority of infants and children are healthy and experience only brief acute pain episodes, however, some have severely painful conditions such as epidermolysis bullosa, osteogenesis imperfecta, cancer, metabolic/neurologic disease, or sickle cell disease, to name a few. Most analgesics are used off-label in pediatric patients, and healthcare providers largely rely on clinical practice guidelines and published sources to inform their use. As such, the pursuit of approved pediatric labeling for analgesic drug products, based on properly designed and conducted studies, is crucial to inform the safe and effective use of these products in pediatrics. For opioid analgesics, approval of pediatric labeling does not create novel uses for these products, but instead provides much needed data in patients who require this treatment.

The Pediatric Research Equity Act (PREA) requires new drug applications (NDAs) and biologic licensing applications (BLAs) or supplements to these applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment of the safety and effectiveness of the drug product in the indication for which the company is seeking in adults unless the applicant has obtained a waiver or deferral of this requirement. The amount of pediatric data needed to fulfill the requirements under PREA varies between applications and is considered on a case-by-case basis. However, some broad principles do apply, for example, in certain situations, effectiveness may be extrapolated from adults to pediatric populations. PREA states that "[i]f the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies."[1]

Our current approach has been to allow extrapolation of efficacy for opioid analgesics from adults to pediatric patients two years of age and older[2] provided that comparable exposures are demonstrated between these two populations. Safety data are still required for this pediatric age group, as safety may not be extrapolated. Consistent with this approach, the requirements for opioid analgesics intended for use in acute pain (i.e., immediate-release opioid analgesics) are to provide pharmacokinetic and safety studies in pediatric patients two years of age and older and pharmacokinetic, safety, and efficacy studies for pediatric patients birth to less than two years of age.

These studies are often conducted post approval, and companies submit a supplement or supplements to the NDA containing the pediatric data intended to fulfill the requirements under PREA along with proposed labeling based on the data. However, companies continue to encounter significant challenges enrolling pediatric populations in analgesic clinical studies due to a variety of reasons, including too few numbers of patients available for study, parental concerns, ethical and logistical challenges (e.g., with respect to study design), etc. The

[1] Refer to draft guidance for industry *How to Comply with the Pediatric Research Equity Act*, available at https://www.fda.gov/media/72274/download, for more information regarding PREA.
[2] Berde CB, et al. Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop. Pediatrics. 2012 Feb;129(2):354-64.

development of opioid analgesics for pediatric patients was discussed at the September 15-16, 2016, Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), the Drug Safety and Risk Management Advisory Committee (DSaRM), and the Pediatric Advisory Committee (PAC). For additional information refer to the following resources (https://www.fda.gov/advisory-committees/advisory-committee-calendar/september-15-16-2016-joint-meeting-anesthetic-and-analgesic-drug-products-advisory-committee-drug):

- FDA Briefing information: https://www.fda.gov/advisory-committees/anesthetic-and-analgesic-drug-products-advisory-committee/briefing-information-september-15-16-2016-joint-meeting-anesthetic-and-analgesic-drug-products
- Presentations: https://www.fda.gov/advisory-committees/anesthetic-and-analgesic-drug-products-advisory-committee/slides-september-15-16-2016-joint-meeting-anesthetic-and-analgesic-drug-products-advisory-committee
- Minutes: https://www.fda.gov/media/100685/download
- Transcripts:
    - https://www.fda.gov/media/101716/download
    - https://www.fda.gov/media/101727/download

When reviewing applications containing pediatric data and proposed labeling, the Division considers the risks and benefits to the individual pediatric pain patient as well the broader public health considerations surrounding opioids and pediatric pain management needs. As one example, the Division is currently reviewing pediatric data and proposed labeling for Opana (oxymorphone hydrochloride) tablets, an immediate-release (IR) formulation of oxymorphone, in the two years and older age group.

2. Pediatric Data for Immediate-Release Opana (oxymorphone hydrochloride) in Patients Two Years of Age and Older

Regulatory History

Opana (oxymorphone hydrochloride) tablets were approved on June 22, 2006 and are indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Opana tablets are an immediate-release formulation of oxymorphone distinct from reformulated Opana ER (oxymorphone hydrochloride) extended-release tablets, which were voluntarily removed from the market at the request of FDA for serious risks related to abuse.[3] The risks surrounding FDA's decision to request the removal of that product were discussed at the March 13-14, 2017, Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee. Refer to https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-meeting-time-and-public-participation-information-joint-meeting-drug-safety-and-risk for a full discussion of those risks.

[3] https://www.fda.gov/news-events/press-announcements/fda-requests-removal-opana-er-risks-related-abuse

The current PREA requirements for Opana tablets are:

- Deferred study of efficacy, safety, and pharmacokinetics (single- and multiple-dose) under PREA for the relief of moderate to severe acute pain where the use of an opioid is appropriate in patients ages 0-2 years
- Deferred study of safety and pharmacokinetics (single- and multiple-dose) under PREA for relief of moderate to severe acute pain where the use of an opioid is appropriate in patients ages 2-17 years

The company submitted a supplement to NDA 21611 for Opana tablets on December 21, 2018, that includes two pediatric pharmacokinetic (PK) and safety studies covering the pediatric age range of 2 to 17 years to fulfill the PREA requirement listed in the second bullet above (PMR 127-3). The company has proposed to include pediatric labeling for these studies in relevant sections of the labeling but is not seeking a pediatric indication.

Clinical Pharmacology Review of the Submitted Data

The Applicant, Endo Pharmaceuticals, Inc., submitted an efficacy prior approval supplement (PAS) for Opana tablets (Supplement 16) to fulfill PREA requirement PMR 127-3 in pediatric patients 2 to 17 years of age. This submission includes the final pediatric study reports; CMC data supporting oxymorphone HCL 1 mg/mL oral solution, which was used in the youngest patients; and proposed labeling changes regarding the pediatric clinical experience.

The Applicant has stated that they do not intend to market or distribute the oxymorphone HCl oral solution, 1 mg/mL. Additionally, the Applicant is not seeking a pediatric indication, nor are there new proposals for pediatric dosing under Dosage and Administration.

The proposed indication remains the same and is stated as: "*For the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate*." However, the Applicant does propose to incorporate the findings from the submitted open-label pediatric studies into revised labeling under the following sections:

- **6.1 Clinical Trials Experience, Clinical Trial Experience in Pediatric Patients 2 Years and Older**: updates include the clinical safety information from pediatric patients 2 years and older

- **8.4 Pediatric Use**: updates include a description of the safety information derived from the pediatric studies

- **12.3 Pharmacokinetics, Absorption**: updates include a statement describing that oxymorphone HCl oral solution was bioequivalent to Opana tablets under fasting conditions in adults

- **12.3 Pharmacokinetics, Specific Populations, Age: Pediatric Population**: updates include a statement regarding 'similar oxymorphone exposure' as well as the 'half-life'

among patients 2 to less than 12 and greater than 12 to 17 years of age and the adult population, based on a weight adjusted basis.

Study design and results

In the pediatric studies, the Applicant used the following formulations:

1. The marketed Opana IR tablets for 12 to 17 years old

2. An oxymorphone oral solution (1 mg/mL) for 2 to 12 years old

Below is a discussion of the conduct and results of the Applicant's three studies assessing the bioavailability, bioequivalence, and, pharmacokinetics of the pediatric formulations. Oxymorphone and its major metabolite, 6-OH-oxymorphone were assayed in the pharmacokinetic (PK) studies. In animal studies, 6-OH-oxymorphone has been shown to have some analgesic bioactivity, but the in vivo levels are less than the parent, oxymorphone, in humans. Therefore, the exposure comparisons between pediatric and adult populations are based on oxymorphone exposure levels.

Study EN3319-101:

Study Title: An open-label, randomized, single dose, two-period, two-sequence crossover; EN3319 5 mg (solution) vs. Opana 5 mg in Healthy Adult Subjects Under Fasted Conditions

Study Description: Adult relative bioavailability/bioequivalence study comparing the pediatric liquid formulation (1 mg/mL) and the Opana tablet IR formulation.

Results from Study EN3319-101: This study was conducted to evaluate the pharmacokinetics of the pediatric solution formulation in adults before use in the pediatric population. The results from Study EN3319-101 indicate that oxymorphone and 6-OH-oxymorphone exposures from EN3319 5 mg (1 mg/mL solution) and Opana 5 mg in healthy adults are bioequivalent.

Study EN3203-010:

Study Title: An Open-Label, Ascending, Two-Part, Single- and Multiple-Dose Evaluation of the Safety, Pharmacokinetics, and Effectiveness of Oxymorphone for Acute Postoperative Pain in Pediatric Subjects Ages greater than 12 to 17

Study Description: An open-label safety, efficacy, and pharmacokinetic (as a secondary parameter in EN3319-302) study in pediatric subjects ages greater than 12 to 17.

The single-dose phase consisted of three ascending doses of oxymorphone IR, given in stepwise order based on the lower dose's ability to demonstrate safety and tolerability:

- 5 mg (equivalent to 0.1 mg/kg for a 50-kg child)
- 10 mg (equivalent to 0.2 mg/kg for a 50-kg child)

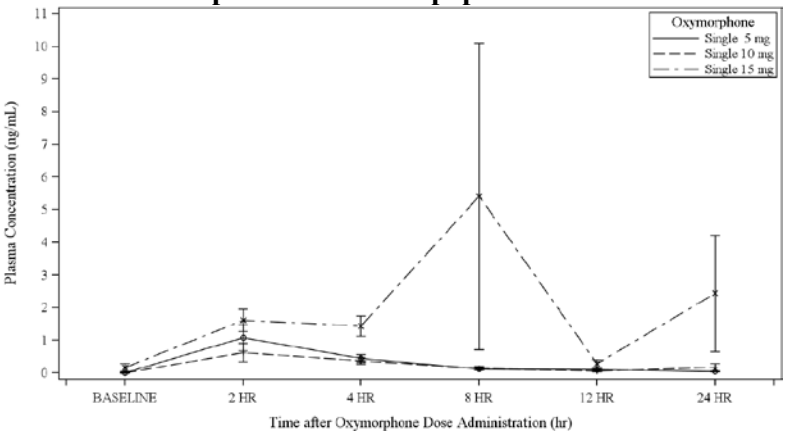
- 15 mg (0.3 mg/kg for a 50-kg child)

The multiple-dose phase also consisted of three ascending doses of oxymorphone IR, given in stepwise order based on the lower dose's ability to demonstrate safety and efficacy. The doses were given every 4 to 6 hours, but, no sooner than every 4 hours and no later than every 6 hours. Doses used in the multiple-dose period were determined from the results of the single-dose period. The Applicant stated that during the multiple-dose phase of this study only trough levels at the beginning of each dose interval were obtained. Additionally, plasma oxymorphone and 6-OH-oxymorphone concentrations were determined at 4-hour intervals, only; therefore, PK parameters were not evaluated.

Results from Study EN3203-010:

The mean oxymorphone plasma concentration versus time profiles after administration of a single dose of Opana IR tablets are shown in Figure 1.

Figure 1: Mean (+/- SE) plasma concentrations of oxymorphone versus time following single-dose treatment in the pharmacokinetic population



Source: Listing 16.2.5.2
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(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3203-010; p. 114/317)

The plasma pharmacokinetic parameters of a single dose of oxymorphone are shown in Table 1.

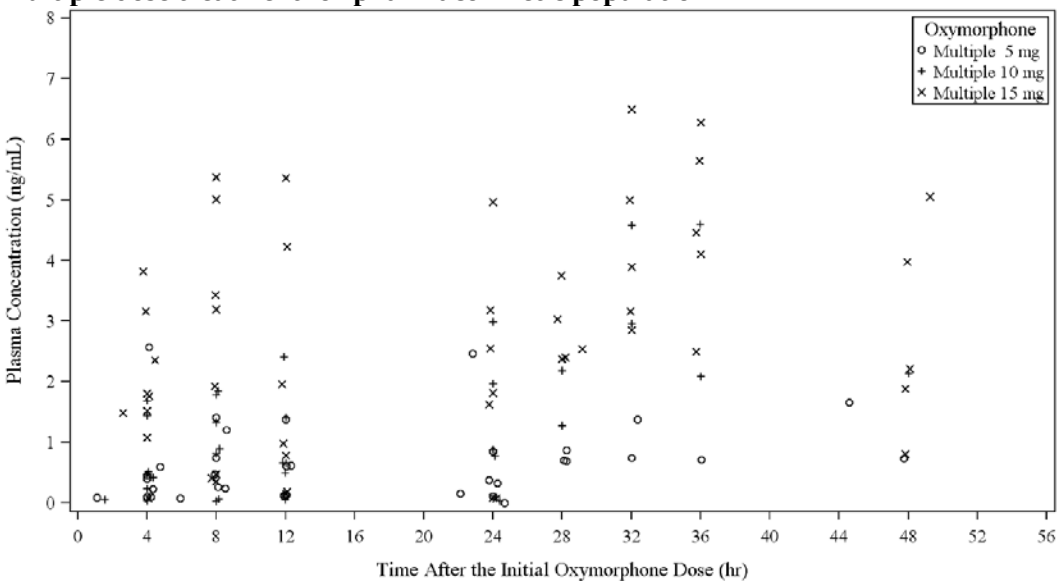
Table 1 Summary of oxymorphone plasma pharmacokinetic parameters of a single dose of oxymorphone by treatment group – pharmacokinetic population

Statistics	Oxymorphone (ng/mL)		
	5 mg (N=11)	10 mg (N=8)	15 mg (N=9)
AUC_{0-t} (ng*hr/mL)			
n	9	6	9
Mean	6.395	3.766	67.040
SD	6.0752	2.2587	150.7979
AUC_{0-inf} (ng*hr/mL)			
n	9	3	8
Mean	7.632	10.223	109.294
SD	6.6828	6.5195	257.5421
Cmax (ng/mL)			
n	9	6	9
Mean	1.243	0.828	5.295
SD	1.2192	0.6892	10.6386
T_{max} (hour)			
n	9	6	9
Median	2.350	2.842	4.000
$t_{½}$ (hour)			
n	9	3	8
Mean	12.099	15.900	19.974
SD	9.9336	18.2533	22.4488

Data Source: Table 14.2.4
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3203-010; p. 48/317)

A scatter plot of plasma concentration of oxymorphone versus dose time by multiple-dose treatment are shown in Figure 2.

Figure 2 Scatter plot of plasma concentration of oxymorphone versus previous dose time by multiple dose treatment for pharmacokinetic population



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Program: FPK2b.sas Output: FPK2b.rtf
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3203-010; p. 116/317)

A summary of observed mean plasma concentrations per the sampling time-points of oxymorphone by treatment (Dose) group after multiple dose are shown in Table 2.

Table 2 Summary of observed oxymorphone mean plasma concentrations per the sampling time-points of oxymorphone by treatment group after multiple dose

Timepoint	Statistics	Oxymorphone (ng/mL)		
		5 mg	10 mg	15 mg
		(N=8)	(N=8)	(N=8)
4 hours	n	8	7	8
	Mean	0.56655	0.69068	1.94886
	SD	0.832757	0.623060	1.171995
8 hours	n	6	7	8
	Mean	0.72122	0.96958	2.52175
	SD	0.493076	0.742611	2.046728
12 hours	n	6	6	7
	Mean	0.49530	0.94882	1.95010
	SD	0.493681	0.839298	2.059903
24 hours	n	7	5	7
	Mean	0.60953	1.33032	2.04354
	SD	0.861570	1.153598	1.735689
28 hours	n	3	4	5
	Mean	0.75157	1.54550	2.82080
	SD	0.105814	0.943873	0.583736
32 hours	n	2	3	5
	Mean	1.06000	3.34100	4.28140
	SD	0.452548	1.103008	1.488950
36 hours	n	1	2	5
	Mean	0.71450	3.34350	4.59860
	SD	-	1.784030	1.468756
48 hours	n	3	1	5
	Mean	0.81028	2.13700	2.78800
	SD	0.809334		1.701034

(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3203-010; p. 132/317)

Study EN3319-302:

Study Title: An Open-Label, Non-randomized, Multicenter, Ascending Dose by Age, Single- and Multiple-Dose Evaluation of the Effectiveness, Safety, and Tolerability of Oxymorphone HCl Immediate-Release Oral Liquid for Acute Postoperative Pain in Pediatric Subjects Ages 2 ≤12

Study Description: An open-label safety, efficacy, and pharmacokinetic (as a secondary parameter in EN3319-302) study in pediatric subjects ages 2 to greater than or equal to 12.

Study EN3319-302 was an open-label, 2-part (single- and multiple-dose), ascending-dose, multicenter study utilizing oxymorphone HCl oral solution (1 mg/mL) in pediatric subjects aged 2 to less than or equal to 12 years with postoperative pain requiring an opioid.

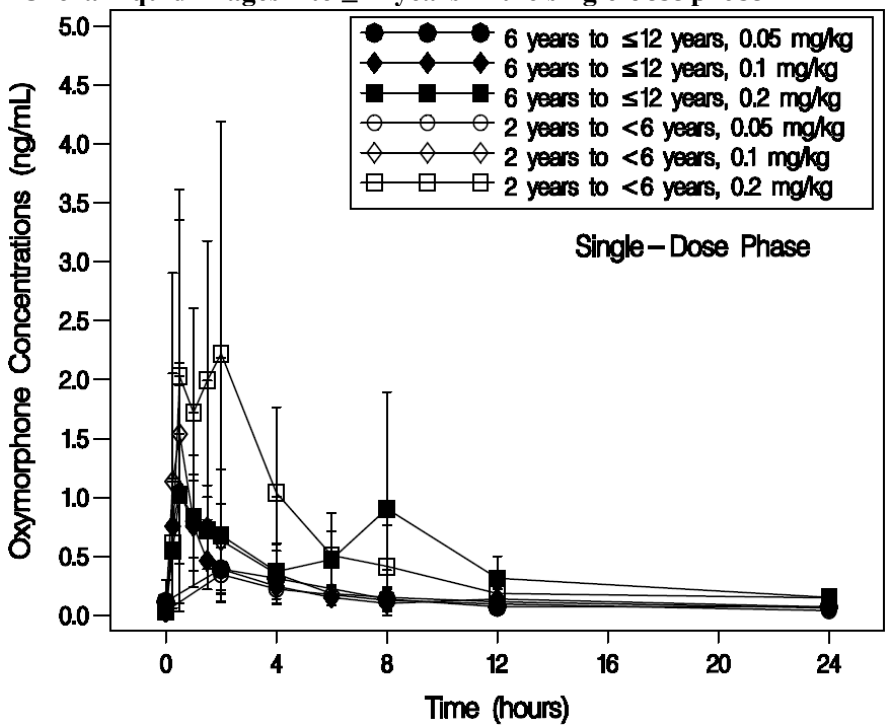
Patients in the single-dose phase, which was comprised initially of three groups of subjects including a 0 to 2 years age group, were given a single dose of oxymorphone HCl oral solution. The Applicant stated that the 0 to 2 years age group was removed due to this group of subjects being studied in another ongoing study. The final two age groups were 2 to less than 6 years and 6 to less than or equal to 12 years. Within each age group, there were three treatment cohorts comprised of three different doses of oxymorphone HCl oral solution, namely, 0.05 mg/kg, 0.1 mg/kg, and 0.2 mg/kg, which were administered following an ascending dose scheme.

It was noted by the Applicant that, at the end of the single-dose phase, an Independent Data Monitoring Committee recommended that a dose of 0.2 mg/kg be used in the Multiple-Dose Phase. Thus, the multiple-dose phase employed only one dose at 0.2 mg/kg. Subjects were dosed approximately every 4 to 6 hours for up to 48 hours.

Results from Study EN3319-302:

The mean oxymorphone plasma concentration versus time profiles after a single dose of oxymorphone HCl oral solution are shown in Figure 3.

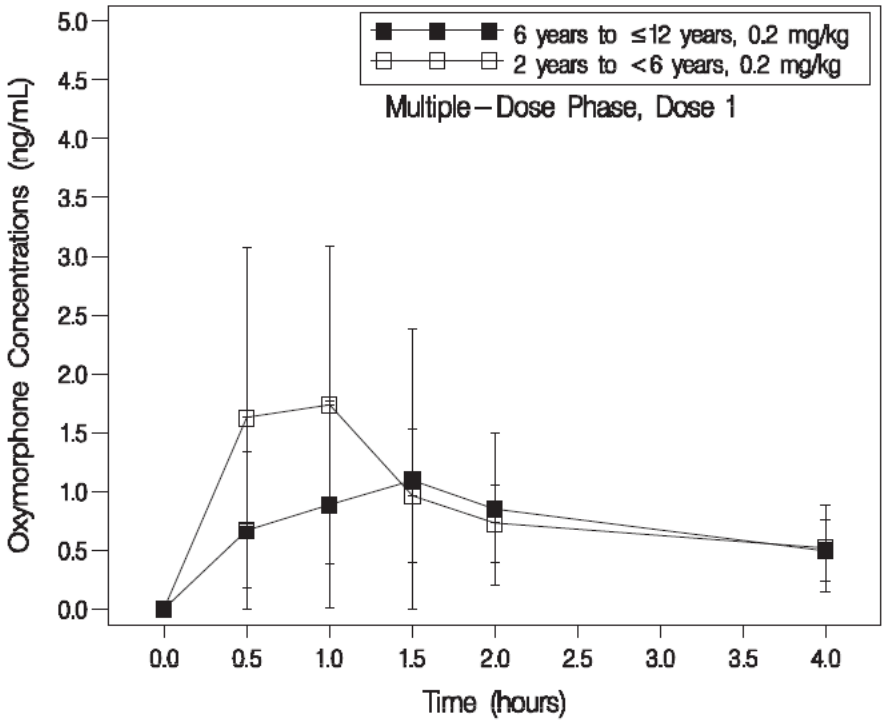
Figure 3 Mean (SD) plasma oxymorphone concentrations following administration of oxymorphone HCl oral liquid in ages 2 to ≤12 years in the single-dose phase



Data Source: Study EN3319-302 Pharmacokinetic Report [Figure 1]
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 53/642)

The mean oxymorphone plasma concentration versus time profiles after Dose 1 in the multiple-dose phase after oxymorphone HCl oral solution administration are shown in Figure 4.

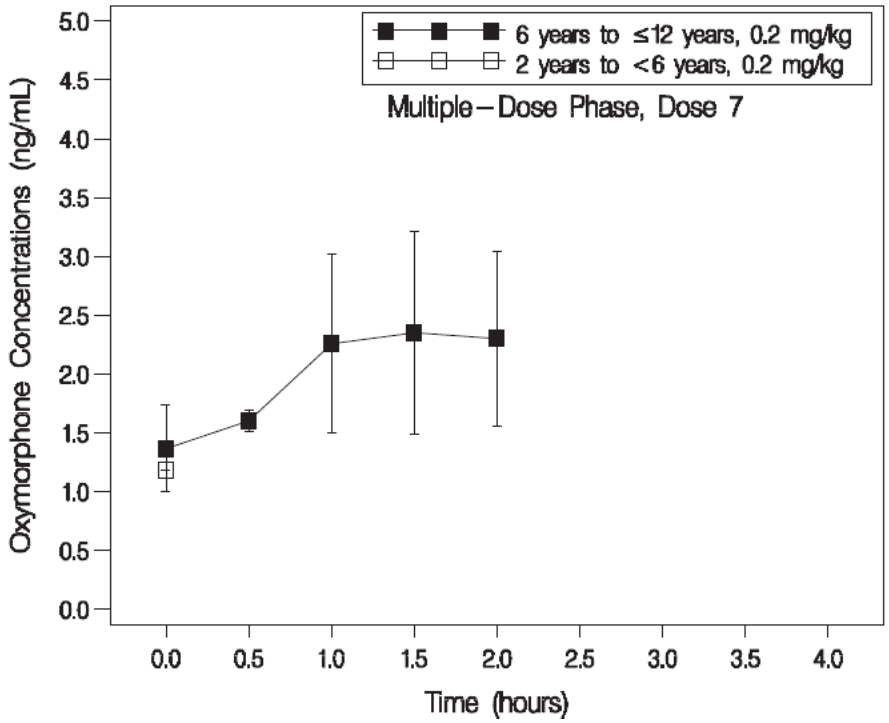
Figure 4 Mean (SD) plasma oxymorphone concentrations following single-dose administration of oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the multiple-dose phase from Dose 1 (linear-linear coordinates)



(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 54/642)

The mean oxymorphone plasma concentration versus time profiles after Dose 7 in the multiple-dose phase after oxymorphone HCl oral solution administration are shown in Figure 5.

Figure 5 Mean (SD) plasma oxymorphone concentrations following single-dose administration of oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the multiple-dose phase from dose 7 (linear-linear coordinates)



(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 55/642)

Summary oxymorphone PK parameters following single-dose administration of 0.05, 0.1, and 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to less than or equal to 12 years in the single-dose phase are shown in Table 3.

Table 3 Summary oxymorphone pharmacokinetic parameters following single-dose administration of 0.05, 0.1, and 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the single-dose phase

	Cmax (ng/mL)	Tmax* (h)	AUC0-t (h*ng/mL)	AUC0-inf (h*ng/mL)	T1/2 (h)
0.05 mg/kg – Children Aged 6 years to ≤12 years					
n	6	6	6	2	2
Mean	0.415	2.95	2.56	.	.
SD	0.211	1.66	2	0.0516	0.232
0.05 mg/kg – Children Aged 2 years to <6 years					
n	7	7	7	2	2
Mean	0.33	2.05	1.69	3.22	5.01
SD	0.217	1.03	0.943	1.56	1.4
0.1 mg/kg – Children Aged 6 years to ≤12 years					
n	6	6	6	2	2
Mean	1.14	1.04	3.01	3.01	7.5
SD	0.847	1.3	0.766	0.946	7.33
0.1 mg/kg – Children Aged 2 years to <6 years					
n	6	6	6	3	3
Mean	1.76	1.45	3.99	3.69	4.38
SD	1.62	1.39	2.09	3.12	2.9
0.2 mg/kg – Children Aged 6 years to ≤12 years					
n	7	7	7	3	3
Mean	1.33	1	5.32	6.92	5.13
SD	0.772	3.17	4.53	4.02	3.16
0.2 mg/kg – Children Aged 2 years to <6 years					
n	6	6	6	2	2
Mean	3.16	1.26	9.37	14.3	4.39
SD	1.65	1.38	5.81	5.01	1.16

Source: Supportive Tables ST-4.1 and ST-4.4 and Appendix I.
. Not determined, or not reported due to insufficient data for reliable estimate.
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 62-64/642)
*Tmax: median

Summary oxymorphone PK parameters following multiple-dose administration of 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to less than or equal to 12 years in the multiple-dose phase from Dose 1 and Dose 7 are presented in Table 4.

Table 4 Summary oxymorphone pharmacokinetic parameters following multiple-dose administration of 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the multiple-dose phase from Dose 1 and Dose 7

	Cmax (ng/mL)	Tmax* (h)	AUC0-t (h*ng/mL)	AUC0-inf (h*ng/mL)	T1/2 (h)
0.2 mg/kg – Children Aged 6 years to ≤12 years – Dose 1					
n	10	10	10	3	3
Mean	1.46	1.55	3.49	4.01	2.18
SD	1.16	0.599	3.22	1.43	0.459
0.2 mg/kg – Children Aged 2 years to <6 years – Dose 1					
n	5	5	5	3	3
Mean	2.58	0.867	3.88	4.53	1.17
SD	1.24	0.622	1.45	2.21	0.632
0.2 mg/kg – Children Aged 6 years to ≤12 years – Dose 7					
n	3	3	3	0	0
Mean	2.66	1.5	4.24	.	.
SD	0.805	1.1	0.9	.	.
0.2 mg/kg – Children Aged 2 years to <6 years – Dose 7					
n	0	0	0	0	0
Mean	.	.	.	.	.
SD	.	.	.	.	.

Source: Supportive Tables ST-4.9 to ST-4.12 and Appendix I.
. Not determined, or not reported due to insufficient data for reliable estimate. (Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p.66-67/642)
*Tmax: median

Clinical Pharmacology Discussion

The exposure comparisons between pediatric and adult populations are based on oxymorphone exposure levels. Table 5 compares single-dose oxymorphone parameters between pediatrics and adults. As a reference, single-dose 6-OH-oxymorphone parameters between pediatrics and adults are also summarized in Table 6.

Table 5 Comparison of oxymorphone pharmacokinetic parameters after a single-dose

			C_{max} (ng/mL)				AUC_{0-t} (ng.h/mL)				AUC_{0-inf} (ng.h/mL)			
Study	**Pop.**	**Dose**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
EN3203-101	**Adults**	**5 mg**	**0.69**	**0.34**	**0.22**	**1.88**	**3.94**	**1.67**	**1.67**	**8.83**	**4.34**	**1.86**	**2.01**	**9.21**
EN3203-010	>12 to 17 y Ped	5 mg	1.24	1.22	0.08	4.00	6.40	6.08	1.18	20.96	7.63	6.68	1.60	22.26
		10 mg	0.83	0.69	0.04	1.96	3.77	2.26	0.12	6.47	10.22	6.525	6.16	17.74
		15 mg	5.30	10.64	0.05	33.55	67.04	150.80	3.30	467.26	109.29	257.54	3.89	746.34
EN3319-302	6 to ≤12 y Ped	0.05 mg/kg	0.42	0.21	0.16	0.73	2.56	2.00	1.25	6.56	2.42	0.052	2.39	2.46
		0.10 mg/kg	1.14	0.85	0.49	2.81	3.01	0.77	2.22	4.35	3.01	0.95	2.34	3.68
		0.20 mg/kg	1.33	0.77	0.46	2.43	5.32	4.53	0.14	12.90	6.92	4.02	3.69	11.40
EN3319-302	2 to <6 y Ped	0.05 mg/kg	0.33	0.22	0.11	0.62	1.69	0.94	0.76	3.69	3.22	1.56	2.12	4.32
		0.10 mg/kg	1.76	1.62	0.42	4.52	3.99	2.09	1.63	7.01	3.69	3.12	1.83	7.29
		0.20 mg/kg	3.16	1.65	1.18	5.60	9.37	5.81	2.69	17.30	14.30	5.01	10.80	17.90

Table 6 Comparison of 6-OH-Oxymorphone pharmacokinetic parameters after a single-dose

			C_{max} (ng/mL)				AUC_{0-t} (ng.h/mL)				AUC_{0-inf} (ng.h/mL)			
Study	**Population**	**Dose**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
EN3203-101	Adults	5 mg	0.76	0.29	0.32	1.36	4.85	2.31	1.34	11.67	6.59	2.50	3.17	11.05
EN3203-010	>12 to 17 y Ped	5 mg	0.31	0.29	0.05	0.96	1.54	1.88	0.28	5.27	4.99	7.57	0.58	18.24
		10 mg	0.49	0.29	0.16	1.02	3.04	1.16	1.38	4.42	8.69	10.24	3.45	26.99
		15 mg	0.94	0.52	0.30	1.87	7.35	3.33	2.34	12.14	12.80	8.84	4.15	34.41
EN3319-302	6 to ≤12 y Ped	0.05 mg/kg	0.10	0.06	0.00	0.16	0.46	0.40	0.00	1.09	1.83	NA	1.83	1.83
		0.10 mg/kg	0.38	0.18	0.18	0.62	1.22	0.76	0.44	2.57	0.54	NA	0.54	0.54
		0.20 mg/kg	0.60	0.51	0.13	1.51	2.64	2.52	0.14	7.45	7.58	5.12	3.95	11.20
EN3319-302	2 to <6 y Ped	0.05 mg/kg	0.10	0.073	0.04	0.25	0.47	0.47	0.04	1.25	1.11	NA	1.11	1.11
		0.10 mg/kg	0.44	0.42	0.17	1.27	1.27	0.64	0.60	2.40	1.76	0.76	0.94	2.78
		0.20 mg/kg	0.59	0.18	0.35	0.80	2.26	1.07	0.33	3.58	2.76	0.40	2.47	3.04

No multiple-dose PK parameter values for oxymorphone or 6-OH-Oxymorphone were generated. Of the three studies submitted in this supplement, multiple-dose PK parameter values were only calculated in Study EN3319-302 after Dose 1 and Dose 7; however, there were too few subjects remaining in the study at the time of Dose 7 to accurately calculate multiple-dose PK parameter values.

Based on the single-dose comparison, the observed C_{max} and AUC values are higher in subjects from 12 to 17 years compared to adults at the 5 mg dose level. It is possible that the higher exposures in 12 to 17 were driven by subjects with a lower body weight.

Among the total of 24 subjects studied (n=9 for 5 mg, n=6 for 10 mg, and, n=9 for 15 mg), two subjects (EN3203-010-0004-1002 (5 mg dose) and EN3203-010-0017-1002 (15 mg dose)) had substantially higher oxymorphone exposure levels. The Applicant investigated these subjects and could find no obvious reasons for the higher exposures. Because the oxymorphone exposure levels for these two subjects are many fold higher than the others, these two subjects may be considered outliers. Therefore, subjects EN3203-010-0004-1002 (5 mg dose) and EN3203-010-0017-1002 (15 mg dose) will be excluded in the overall assessment.

Additionally, in order to compare with 2 to 12-year-old subjects, the dose column in Table 5 was revised to dose/kg and is presented in Table 7. Note subjects EN3203-010-0004-1002 (5 mg dose) and EN3203-010-0017-1002 (15 mg dose) in 12 to 17 were excluded from the PK parameter calculations in Table 7, while they were not excluded from those in Table 5.

Table 7 Comparison of oxymorphone pharmacokinetic parameters after a single-dose presented as dose/kg body weight

			C_{max} (ng/mL)				AUC_{0-t} (ng.h/mL)				AUC_{0-inf} (ng.h/mL)			
Study	**Population**	**Dose**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
EN3203-101	**Adults**	**5 mg**	**0.69**	**0.34**	**0.22**	**1.88**	**3.94**	**1.67**	**1.67**	**8.83**	**4.34**	**1.86**	**2.01**	**9.21**
EN3203-010	>12 to 17 y Ped	**0.08 mg/kg***	**0.90**	0.69	0.08	1.84	**4.57**	2.84	1.18	9.74	**5.80**	4.08	1.60	14.44
		0.16 mg/kg*	**0.83**	0.69	0.04	1.96	**3.77**	2.26	0.12	6.47	10.22#	6.52#	6.16#	17.74#
		0.23 mg/kg*	1.76	1.02	0.49	3.64	17.01	15.68	3.30	52.21	18.29	9.10	3.89	28.60
EN3319-302	6 to ≤12 y Ped	0.05 mg/kg	0.42	0.21	0.16	0.73	2.56	2.00	1.25	6.56	2.42	0.052	2.39	2.46
		0.10 mg/kg	1.14	0.85	0.49	2.81	3.01	0.77	2.22	4.35	3.01	0.95	2.34	3.68
		0.20 mg/kg	1.33	0.77	0.46	2.43	5.32	4.53	0.14	12.90	6.92	4.02	3.69	11.40
EN3319-302	2 to <6 y Ped	0.05 mg/kg	0.33	0.22	0.11	0.62	1.69	0.94	0.76	3.69	3.22	1.56	2.12	4.32
		0.10 mg/kg	1.76	1.62	0.42	4.52	3.99	2.09	1.63	7.01	3.69	3.12	1.83	7.29
		0.20 mg/kg	3.16	1.65	1.18	5.60	9.37	5.81	2.69	17.30	14.30	5.01	10.80	17.90

*Dose: average of dose by BW; 5 mg = ~0.08 mg/kg; 10 mg = ~0.16 mg/kg; 15 mg = ~0.23 mg/kg; Subjects EN3203-010-0004-1002 (5 mg dose) and EN3203-010-0017-1002 (15 mg dose) excluded.
#N=3

In summary, based on Table 7, it is reasonable to conclude that a 5 mg single dose in 12 to 17-year-old subjects will provide similar oxymorphone exposure to that of a 5 mg single dose in adults. Similarly, in 2 to less than 6 and 6 to less than or equal to 12 year old subjects, a dose between 0.05 and 0.1 mg/kg, (e.g., 0.075 mg/kg [based on oxymorphone's dose proportional behavior from 5 to 20 mg under both single- and steady-state conditions in adults (Opana IR Prescribing Information)]), provides similar oxymorphone exposures to that of a 5 mg single dose in adults. Lastly, a cross study/information comparison from the submitted information suggests that the half-life of oxymorphone in the 12 to 17 age group is longer (observed half-life from Study EN3203-010: range 12 - 20 hours in 12-17 years old) and 2 to less than 12 years old is shorter (observed half-life from Study EN3319-302: range 4.4- 7.5 hours in 2 to less than 12 years old) than adults (observed half-life from Opana IR Prescribing Information: range 7.25 to 9.43 hours in adults).

Clinical Review of the Submitted Data

Key features of the two pediatric PK and safety studies are summarized in the table below.

Summary of Study Design for the Two Pediatric studies

Study	EN3319-302 (age 2-12 years)	EN3203-010 (age >12 to 17 years)
Title	An Open-Label, Non-randomized, Multicenter, Ascending Dose by Age, Single- and Multiple-Dose Evaluation of the Effectiveness, Safety, and Tolerability of Oxymorphone HCl Immediate-Release Oral Liquid for Acute Postoperative Pain in Pediatric Subjects	An Open-Label, Ascending, Two-Part, Single- and Multiple-Dose Evaluation of the Safety, Pharmacokinetics, and Effectiveness of Oxymorphone for Acute Postoperative Pain in Pediatric Subjects
Formulation	Oral liquid	5 and 10 mg tablet
Age group	3 age groups: 6-12, 2 to <6 and 0-<2 years, where age 0-<2 years terminated early & was limited to single dose	One age group
Design	Open-label Single-dose and multiple-dose Dose escalation (3 levels)	Open-label Single-dose and multiple-dose Dose escalation (3 levels)
Pain model	Postoperative pain	Postoperative pain
Population	Age 2-12 requiring oral opioid to treat acute postoperative pain of various etiologies	Age >12-17 requiring an opioid to treat postoperative pain of various etiologies
Baseline PI	Scale: FPS-R (6-12) , FLACC (2-<6)	≥40 (100-mm VAS)
Treatment	Oxymorphone oral liquid Single dose at 0.05, 0.1, & 0.2 mg/kg Multiple dose 0.2 mg/kg q4-6h for up to 48 hours	Opana 5-mg, 10-mg, and 15-mg Single dose at 5, 10, & 15 mg Multiple dose at 5, 10, & 15 mg q4-6h for up to 48 hours
Rescue	Standard care (encouraging one-hour waiting)	Standard care (encouraging one-hour waiting)
PK sampling	0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, & 24 hours post single dose; 0, 0.5, 1, 1.5, and 2 hours post Dose 1, immediately prior to Doses 2, 3, 4, 5, 6, 7, and at 0.5, 1, 1.5, and 2 hours post-Dose 7 in the multiple- dose period	0, 2, 4, 8, 12, & 24 hours post single dose; 0, 4, 8, 12, 24, 28, 32, 36, & 48 hours post the initial dose in the multiple- dose period
Safety	Adverse events (AEs) Respiratory function (apnea monitoring & oxygen saturation) Neurological function Vital signs Clinical laboratory tests (baseline, 24-h post single dose, and 48-h post the initial dose in the multiple- dose period)	Adverse events (AEs) Respiratory function (apnea monitoring & oxygen saturation) Neurological function Vital signs (frequent) Clinical laboratory tests (baseline, 24-h post single-dose, 48-h post the initial dose in the multiple- dose period)
Efficacy data	• Pain Intensity (PI) at 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, & 24 hours post single dose • PI at 0, 0.5, 1, 1.5, and 2 hours post initial dose and predose during repeated dosing • Rescue data	• PI at 0, 0.25, 0.5, 1, 2, 3, 4, & 6 hours post single dose • PI at 0, 0.25, 0.5, 1, 2, 3, 4, (6) hours post initial dose and predose during repeated dosing • Rescue data

Source: individual study reports and protocols

Study Results

Patient disposition

In Study EN3203-010, about 35% (20 of 58) of the greater than 12 to 17 years age group completed the study. Early discontinuation accounted for about two thirds of the study population, including 22 of 33 (67%) patients in the single-dose phase and 16 of 25 (64%) patients in the multiple-dose phase, mostly (33 of 38 who had discontinued) due to lack of efficacy. The other cases of early dropouts were due to adverse events in two cases (both in multiple-dose phase), withdrew consent/assent in two cases, and Investigator's decision in one case. About 90% (52 of 58) were Included in the PK analysis.

Patient Disposition, Study EN3203-010

Study (EN3203-010) Patient Disposition							
	Single dose			Multiple dose			***Overall***
Opana tablet	**5 mg**	**10 mg**	**15 mg**	**5 mg**	**10 mg**	**15 mg**	
Enrolled (safety population)	13	9	11	9	8	8	*58*
Completed	7 (53.8)	0	4 (36.4)	3 (33.3)	1 (12.5)	5 (62.5)	*20 (34.5)*
Discontinued	6 (46.2)	9 (100)	7 (63.6)	6 (66.7)	7 (87.5)	3 (37.5)	*38 (65.5)*
Reasons for discontinuation							
Lack of efficacy	6 (46.2)	9 (100)	6 (54.5)	4 (44.4)	6 (75.0)	2 (25.0)	***33 (56.9)***
Adverse event	0	0	0	1 (11.1)	0	1 (12.5)	*2 (3.4)*
Withdrew consent/assent	0	0	1 (9.1)	1 (11.1)	0	0	*2 (3.4)*
Investigator's decision	0	0	0	0	1 (12.5)	0	*1 (1.7)*
Included in PK analysis	11 (84.6)	8 (88.9)	9 (81.8)	8 (88.9)	8 (100)	8 (100)	*52 (89.7)*

Source: Table 7 on page 33 and Table 8 on page 34 of the study report for EN3203-010

In Study EN3319-302, most patients (41 of 45, or 91%) in the two age groups of 6 to less than or equal to 12 and 2 to less than 6 years completed the single-dose phase of the study. There were four cases of early discontinuation, including two cases of withdrawal by subject, one case of lack of efficacy, and one case of other reason.

Patient Disposition, Study EN3319-302, single-dose phase

Study (EN3319-302) Patient Disposition								
Age group	**6 to ≤12 years**			**2 to <6 years**			**0 to <2 years**	**Overall**
Oxymorphone solution, **mg/kg**	**0.05**	**0.10**	**0.20**	**0.05**	**0.10**	**0.20**	**0.05**	
Enrolled (safety population)	6	6	7	7	6	6	7	45
Completed	6 (100.0)	6 (100.0)	5 (71.4)	7 (100.0)	6 (100.0)	6 (100.0)	5 (71.4)	41 (91.1)
Discontinued	0	0	2 (28.6)	0	0	0	2 (28.6)	4 (8.9)
Reasons for discontinuation								
Withdrawal by subject	0	0	1 (14.3)	0	0	0	1 (14.3)	2 (4.4)
Lack of efficacy	0	0	0	0	0	0	1 (14.3)	1 (2.2)
Other	0	0	1 (14.3)	0	0	0	0	1 (2.2)
Included in PK analysis	6	6	7	7	6	6	7	45

Source: Table 8 on page 48 of the study report for EN3319-302

In the multiple-dose phase, nine of 16 patients (7 of the 10 patients in the 6 to less than or equal to 12 years age group and two of the six patients in the 2 to less than 6 years age group) completed the study. There were seven cases of early discontinuation due to adverse events in three cases, physician's decision in three cases, and withdrawal by subject in one case in the two age groups (refer to table below for details per age group).

Patient Disposition, Study EN3319-302, multiple-dose phase

Study (EN3319-302) Patient Disposition			
Age group	**6 to ≤12 years**	**2 to <6 years**	**Overall**
Oxymorphone solution, multiple-dose	**0.20 mg/kg**	**0.20 mg/kg**	
Enrolled (safety population)	10	6	16
Completed	7 (70.0)	2 (33.3)	9 (56.3)
Discontinued	3 (30.0)	4 (66.7)	7 (43.7)
Reasons for discontinuation			
Adverse Event	2 (20.0)	1 (16.7)	3 (18.8)
Physician's decision	1 (10.0)	2 (33.3)	3 (18.8)
Withdrawal by Subject	0	1 (16.7)	1 (6.3)
Included in PK analysis	10	5 (83.3)	15 (93.8)

Source: Table 9 on page 49 of the study report for EN3319-302

Protocol deviations

In Study EN3203-010, pediatric patients aged greater than 12 to 17 years who had at least one protocol deviation included 17 of 33 (52%) enrolled in the single-dose phase and 21 of 25 (84%) enrolled in the multiple-dose phase. The deviation categories involved mostly failure to adhere to assessment schedule, especially in terms of missing vital signs and missing respiratory assessments according to the Applicant's submission dated June 5, 2019.

The proportions of subjects with protocol deviations and the counts would be much higher if the cases of missing clinical lab tests were also included in the table.

Protocol Deviation, Study EN3203-010

Study EN3203-010 Protocol Deviations							
	Single dose			**Multiple dose**			**Total**
Opana tablet	5 mg	10 mg	15 mg	5 mg	10 mg	15 mg	
N	13	9	11	9	8	8	58
# Patients with ≥ 1 deviation	8 (61.5)	4 (44.4)	5 (45.5)	8 (88.9)	6 (75.0)	7 (87.5)	**38 (65.5)**
Counts of specific deviation*							
Inclusion/Exclusion Criteria	3	1	1	1	2	0	8
Failure to adhere to assessment schedule	23	10	19	35	27	19	133
Vital Signs and Respiratory Assessment missing	**15**	**7**	**13**	**21**	**19**	**13**	**88**
Vital Signs missing	**5**	**2**	**4**	**6**	**1**	**2**	**20**
Respiratory Assessment missing	**1**	**0**	**1**	**2**	**6**	**2**	**12**
Physical Examination Missing	1	1	0	2	0	0	4
PK Sampling Missing	1	0	1	2	0	0	4
Pain Assessment Missing	0	0	0	2	1	2	5
Total	26	11	20	36	29	19	141

* each category may have multiple deviations for a single patient
Source: Table 1 on page 3 of the Response to Information Request (IR) submitted on April 1, 2019.
Table 1 on pages 1-2 of the Response to Information Request (IR) submitted on June 5, 2019.

In Study EN3319-302, all 61 pediatric patients in both age groups of 6 to less than or equal to 12 and 2 to less than 6 years had at least one protocol deviation. The deviation categories involved mostly failure to adhere to assessment schedule, especially in terms of missing laboratory test results (baseline and/or follow-up test), vital signs, respiratory and neurological assessments, and missing PK sampling.

Protocol Deviations, Study EN3319-302, By Age Group (6-12, 2-<6, 0-<2 years)

Study EN3319-302 Protocol Deviations					
	Single dose			**Multiple dose**	**Total**
Oxymorphone oral solution	0.05 mg/kg	0.10 mg/kg	0.20 mg/kg	0.20 mg/kg	
N (age groups: 6-12, 2-<6, 0-<2 years)	20 (6/7/7) Total (6-12 / 2-<6 / 0-<2y)	12 (6/6) Total (6-12 / 2-<6 y)	13 (7/6) Total (6-12 / 2-<6 y)	16 (10/6) Total (6-12 / 2-<6 y)	61(29/25/7) Total (6-12 / 2-<6 / 0-<2 y)
# Patients with ≥ 1 deviation	20 (100%)	12 (100%)	13 (100%)	16 (100%)	61 (100%)
Counts of specific deviation					
Good Clinical Practice	2	0	3	5	10
Informed Consent Form Process	7	1	2	4	14
Inclusion/Exclusion Criteria	0	3	3	1	7
Investigational Product	0	0	0	9	9
Failure to adhere to assessment schedule	186 **(58/63/65)**	60 (20/40)	58 (37/21)	64 (42/22)	368 (157/146/65)
Clinical Laboratory Tests (lab)	**60 (19/20/21)**	**19** (6/13)	**23** (12/11)	**20** (11/9)	**122** (48/53/21)
Lab: Chemistry and/or Hematology Missing	40 (13/13/14)	14 (3/11)	16 (9/7)	16 (8/8)	86 (33/39/14)
Lab: Urine Drug Screen Missing	20 (6/7/7)	5 (3/2)	7 (3/4)	4 (3/1)	36 (15/14/7)
Vital Signs (VS)	**31 (8/12/11)**	**11** (3/8)	**11** (6/5)	**7** (4/3)	**60** (21/28/11)
VS: Missing	31 **(8/12/11)**	6 (3/3)	10 (5/5)	7 (4/3)	54 (20/23/11)
VS: Incomplete	0	4 (0/4)	1	0	5
VS: Timing error	0	1	0	0	1
Respiratory Assessment missing	**20** (6/7/7)	**4** (1/3)	**5** (5/0)	**3** (1/2)	**32** (13/12/7)
Neurological Assessment missing	**20** (6/7/7)	**4** (0/4)	**2** (2/0)	**2** (1/1)	**28** (9/12/7)
VS and Respiratory Assessment missing	0	4 (0/4)	0	0	4
Respiratory & Neurological Assessment missing	0	0	0	1	1
Physical Exam (PE)					
PE Incomplete	0	1	0	0	1
PE Missing	0	1	0	0	1
PE Timing Error	0	0	0	1	1
PK Sampling missing	**20** (6/7/7)	**5** (4/1)	**7** (5/2)	**11** (8/3)	**43** (23/13/7)
Food Consumption Missing	3	0	0	1	4
Pain Assessment missing	**21** (7/7/7)	**11** (6/5)	**10** (7/3)	**18** (14/4)	**60** (34/19/7)
Follow Up Visit Missing	11 (6/3/2)	0	0	0	11
Failure to adhere to visit window	0	0	0	1	1
Protocol Adherence – Other	2	0	1	0	3
Total	197	64	67	84	412

Source: Table 2 on page 3 of the Response to Information Request (IR) submitted on April 1, 2019.
Table 2 to 5 on pages 4-6 of the Response to Information Request (IR) submitted on June 5, 2019.

Demographics and baseline characteristics

In the single-dose phase of Study EN3203-010, the study population aged greater than 12 to 17 years consisted of 73% female, 85% White, and 100% Non-Hispanic. Mean age, weight, height, and BMI at baseline were basically balanced between the three dose groups of 5, 10, and 15 mg. Ranges of baseline weight, height, and BMI varied among the groups.

In the multiple-dose phase, the study population consisted of 56% female, 88% White, and 88% Non-Hispanic. Mean age, weight, height, and BMI at baseline were basically balanced between the three dose groups. Ranges of baseline weight, height, and BMI varied among the groups.

Demographics and Baseline Characteristics, Study EN3203-010

Study EN3203-010, age >12 to 17 years								
Opana tablet	**Single dose**				**Multiple dose**			
	5 mg	**10 mg**	**15 mg**	**Subtotal**	**5 mg**	**10 mg**	**15 mg**	**Subtotal**
# Patients	N=13	N=9	N=11	N=33	N=9	N=8	N=8	N=25
Sex								
Male	4 (30.8%)	2 (22.2%)	3 (27.3%)	9 (27.3%)	5 (55.6%)	2 (25.0%)	4 (50.0%)	11 (44.0%)
Female	9 (69.2%)	7 (77.8%)	8 (72.7%)	24 (72.7%)	4 (44.4%)	6 (75.0%)	4 (50.0%)	14 (56.0%)
Age (years)								
Mean (SD)	14.9 (1.71)	15.3 (1.66)	14.6 (1.63)	14.9 (1.64)	15.0 (0.71)	15.3 (1.58)	15.5 (1.07)	15.2 (1.13)
Median	15.0	16.0	15.0	15.0	15.0	15.5	16.0	15.0
Min, max	12, 17	13, 17	12, 17	12, 17	14, 16	13, 17	14, 17	13, 17
Race								
White	11 (84.6%)	7 (77.8%)	10 (90.9%)	28 (84.8%)	9 (100%)	7 (87.5%)	6 (75.0%)	22 (88.0%)
Black or African American	2 (15.4%)	2 (22.2%)	1 (9.1%)	5 (15.2%)	0	1 (12.5%)	0	1 (4.0%)
Multiracial	0	0	0	0	0	0	2 (25.0%)	2 (8.0%)
Ethnicity								
Hispanic	0	0	0	0	2 (22.2%)	0	1 (12.5%)	3 (12.0%)
Not Hispanic	13 (100%)	9 (100%)	11 (100%)	33 (100%)	7 (77.8%)	8 (100%)	7 (87.5%)	22 (88.0%)
Weight (kg)	N=13	N=9	N=11	N=33	N=9	N=8	N=8	N=25
Mean (SD)	69.94 (22.648)	70.14 (15.016)	68.45 (16.197)	69.50 (18.201)	63.70 (11.141)	60.78 (7.322)	68.90 (15.709)	64.43 (11.845)
Median	65.00	70.70	66.00	66.00	60.00	63.10	64.45	63.00
Min, Max	33.9, 128.8	51.9, 99.3	45.4, 88.4	33.9, 128.8	53.3, 81.0	45.4, 68.0	51.2, 94.5	45.4, 94.5
Height (cm)	N=13	N=8	N=9	N=30	N=9	N=8	N=8	N=25
Mean (SD)	162.00 (8.700)	167.76 (7.462)	159.44 (6.189)	162.77 (8.118)	168.23 (8.823)	162.46 (9.374)	168.05 (7.138)	166.33 (8.589)
Median	162.50	168.35	160.20	162.75	168.00	161.00	166.50	163.80
Min, Max	152.0, 185.7	159.0, 179.0	146.5, 166.5	146.5, 185.7	156.0, 182.2	148.0, 173.5	159.6, 177.3	148.0, 182.2
BMI (kg/m^2)	N=13	N=8	N=9	N=30	N=9	N=8	N=8	N=25
Mean (SD)	26.19 (5.835)	25.15 (7.069)	27.38 (6.963)	26.27 (6.345)	22.52 (3.720)	23.11 (3.012)	24.26 (4.556)	23.26 (3.723)
Median	24.62	22.68	24.24	24.46	21.25	23.70	22.44	21.70
Min, Max	14.1, 37.4	19.3, 39.3	20.4, 41.2	14.1, 41.2	18.9, 30.0	18.4, 26.9	20.0, 30.6	18.4, 30.6

Source: Table 9 on pages 36-37 of the study report for EN3203-010

Demographic and baseline characteristics for Study EN3319-302 are summarized by age group below. In the single-dose phase, the study population for the age group of 6 to 12 years consisted of 47% female, 68% White, and 95% Non-Hispanic. Mean age, weight, height, and BMI at baseline were basically balanced between the three dose groups of 0.05, 0.10, and 0.20 mg/kg. Ranges of baseline weight, height, and BMI varied among the groups.

In the multiple-dose phase the study population consisted of 50% female, 70% White, and 100% Non-Hispanic. All ten patients received the 0.20 mg/kg dose.

Demographics and Baseline Characteristics, Age 6-12 Years, Study EN3319-302

Study (EN3319-302), Age 6 to ≤12 years					
	Single dose				Multi dose
Oxymorphone oral solution	**0.05 mg/kg**	**0.10 mg/kg**	**0.20 mg/kg**	**Subtotal**	**0.20 mg/kg**
# Patients	N=6	N=6	N=7	N=19	N=10
Sex					
Male	5 (83.3)	4 (66.7)	1 (14.3)	10 (52.6)	5 (50.0)
Female	1 (16.7)	2 (33.3)	6 (85.7)	9 (47.4)	5 (50.0)
Age (years)				19	10
Mean (SD)	8.3 (1.75)	8.7 (1.86)	9.0 (2.16)	8.7 (1.86)	9.6 (1.90)
Median	7.5	9.0	9.0	9.0	9.5
Min, max	7, 11	6, 11	6, 12	6, 12	7, 12
Race					
White	4 (66.7)	3 (50.0)	6 (85.7)	13 (68.4)	7 (70.0)
Black or African American	2 (33.3)	1 (16.7)	0	3 (15.8)	3 (30.0)
Asian	0	2 (33.3)	0	2 (10.5)	0
American Indian or Alaska Native	0	0	1 (14.3)	1 (5.3)	0
Ethnicity					
Hispanic	0	0	1 (14.3)	1 (5.3)	
Not Hispanic	6 (100.0)	6 (100.0)	6 (85.7)	18 (94.7)	10 (100.0)
Weight (kg)	N=6	N=6	N=7	19	10
Mean (SD)	35.25 (11.725)	30.33 (17.731)	37.26 (20.613)	34.44 (16.615)	41.81 (18.103)
Median	39.80	23.45	33.10	33.10	38.80
Min, Max	20.1, 46.4	14.7, 64.2	19.7, 80.8	14.7, 80.8	20.5, 75.0
Height (cm)	N=6	N=5	N=7	18	10
Mean (SD)	129.83 (14.442)	130.54 (19.704)	130.80 (16.645)	130.41 (15.832)	141.61 (14.794)
Median	131.00	131.00	125.00	130.70	139.00
Min, Max	113.0, 153.0	98.5, 149.8	110.0, 158.1	98.5, 158.1	120.0, 163.7
BMI (kg/m^2)	N=6	N=5	N=7	18	10
Mean (SD)	20.35 (4.371)	17.52 (6.354)	20.59 (6.044)	19.66 (5.466)	20.03 (5.443)
Median	20.25	15.20	19.20	18.55	17.90
Min, Max	15.7, 26.6	12.8, 28.6	13.9, 32.3	12.8, 32.3	14.2, 30.7

Source: Table 5 and 6 on pages 44-46 of the study report for EN3319-302

For the age group of 2 to less than 6 years in the single-dose phase, the study population consisted of 58% female, 74% White, and 90% Non-Hispanic. Mean age, weight, height, and BMI at baseline were basically balanced between the three dose groups of 0.05, 0.10, and 0.20 mg/kg. Ranges of baseline weight, height, and BMI varied among the groups.

In the multiple-dose phase the study population consisted of 100% male, 83% White, and 100% Non-Hispanic. All six patients received the 0.20 mg/kg dose.

Demographics and Baseline Characteristics, Age 2 to <6 Years, Study EN3319-302

Study (EN3319-302), Age 2 to <6 years					
	Single dose				**Multi dose**
Oxymorphone oral solution	**0.05 mg/kg**	**0.10 mg/kg**	**0.20 mg/kg**	**Subtotal**	**0.20 mg/kg**
# Patients	N=7	N=6	N=6	N=19	N=6
Sex					
Male	5 (71.4)	3 (50.0)	0	8 (42.1)	6 (100.0)
Female	2 (28.6)	3 (50.0)	6 (100.0)	11 (57.9)	0
Age (years)				19	6
Mean (SD)	3.4 (1.27)	3.5 (1.38)	3.5 (1.38)	3.5 (1.26)	3.8 (1.17)
Median	3.0	3.5	3.5	3.0	4.0
Min, max	2, 5	2, 5	2, 5	2, 5	2, 5
Race					
White	4 (57.1)	4 (66.7)	6 (100.0)	14 (73.7)	5 (83.3)
Black or African American	3 (42.9)	1 (16.7)	0	4 (21.1)	1 (16.7)
Asian	0	1 (16.7)	0	1 (5.3)	0
Ethnicity					
Hispanic	0	0	2 (33.3)	2 (10.5)	
Not Hispanic	7 (100.0)	6 (100.0)	4 (66.7)	17 (89.5)	6 (100.0)
Weight (kg)	N=7	N=6	N=6	19	6
Mean (SD)	18.76 (4.026)	15.77 (4.303)	17.88 (4.869)	17.54 (4.336)	17.83 (2.701)
Median	18.20	14.70	17.65	17.40	16.70
Min, Max	12.7, 24.2	11.4, 22.8	12.7, 26.2	11.4, 26.2	16.0, 23.1
Height (cm)	N=7	N=6	N=5	18	5
Mean (SD)	106.36 (10.111)	96.82 (11.618)	107.42 (15.752)	103.47 (12.562)	101.06 (6.026)
Median	105.00	95.25	108.50	101.30	104.00
Min, Max	93.0, 120.5	82.5, 117.5	84.0, 124.0	82.5, 124.0	91.0, 105.8
BMI (kg/m^2)	N=7	N=6	N=5	18	5
Mean (SD)	16.43 (1.568)	16.70 (2.948)	16.24 (2.293)	16.47 (2.167)	17.78 (2.575)
Median	16.00	16.30	16.30	16.20	16.30
Min, Max	14.7, 18.6	14.0, 22.3	12.7, 18.5	12.7, 22.3	15.6, 21.4

Source: Table 5 and 6 on pages 44-46 of the study report for EN3319-302

For the age group of 0 to less than 2 years, the study population consisted of 86% male, 86% White, and 100% Non-Hispanic. All seven patients received a single dose of study medication at 0.05 mg/kg.

Demographics and Baseline Characteristics, Age 0 to <2 Years, Study EN3319-302

Study (EN3319-302), Age 0 to < 2 years	
Treatment	Oxymorphone oral solution **0.05 mg/kg**
# Patients	N=7
Sex	
Male	6 (85.7)
Female	1 (14.3)
Age (years)	
Mean (SD)	0.4
Median	0.53
Min, max	<1
Race	
White	6 (85.7)
Black or African American	1 (14.3)
Ethnicity	
Hispanic	0
Not Hispanic	7 (100.0)
Weight (kg)	
Mean (SD)	9.10 (3.106)
Median	8.70
Min, Max	4.0, 12.4
Height (cm)	
Mean (SD)	72.93 (9.760)
Median	73.00
Min, Max	55.0, 86.0
BMI (kg/m^2)	
Mean (SD)	16.51 (2.554)
Median	16.80
Min, Max	13.2, 20.7

Source: Table 5 on pages 44-45 of the study report for EN3319-302.

Safety Results

Deaths

No deaths were reported in any study.

Serious adverse events

Serious Adverse Events (SAEs) are listed by age group and dosage as shown in the table below. Seven SAEs were reported in the two pediatric studies, three in the age group greater than 12 to 17 years, three in the age group 6 to 12 years, and one in the age group 2 to less than 6 years.

List of SAEs in Pediatric Studies

Age Groups	**Age >12–17 years (n=58)**			**Age 6–≤12 years (n=29)**			**Age 2–<6 years (n=25)**			**Age 0–<2 years (n=7)**
Dose level	5 mg	10 mg	15 mg	0.05 mg/kg	0.1 mg/kg	0.2 mg/kg	0.05 mg/kg	0.1 mg/kg	0.2 mg/kg	0.05 mg/kg
Single dose	13	9	11	6	6	7	7	6	6	7
SAEs		***1***	***1***		***1***		***1***			
Multiple dose	9	8	8			10			6	
SAEs	***1***					***2***				

Source: Individual study reports.

Case narratives for SAEs were summarized in terms of exposure, SAE type, brief description of the events leading to SAE, concomitant medication, outcome of SAE, and the relationship of SAE with the study drug as shown in the table below. The seven SAEs included one case of atelectasis and fat embolism; one case of failure of spinal implant; one case of anemia, unequal pupils, blurred vision, and headache; one case of neutropenia and postoperative fever; one case of postoperative joint dislocation; one case of abdominal abscess; one case of wound dehiscence. All the SAEs resolved, mostly with treatments targeted at the SAEs, and were considered unlikely to be related to the study drug based on the case narratives provided.

SAE Case Summary Based on Narratives

Patient	Study drug	SAE	Brief description	Concomitant medication	Outcome of SAE	Related to study drug
Study EN3203-010						
Age 17 white female	Opana 10 mg single dose	Atelectasis and fat embolism	Had left femur fracture undergoing surgery for intramedullary nailing, developed acute lung injury from fat emboli syndrome, and had bilateral basal atelectasis on chest X-ray	IV morphine, seretide, oxygen, paracetamol, methocarbamol, hydromorphone, fentanyl, docusate, and enoxaparin	Resolved with treatment	Unlikely
Age 12 white female	Opana 15 mg single dose	Failure of spinal implant	Underwent posterior spinal fusion surgery for severe idiopathic adolescent scoliosis, took one dose of study medication for leg pain, and discovered problems related to multiple screws on CT scan.	Cefazolin, diphenhydramine, Senokot-S, diazepam, macrogol, ketamine, hydromorphone, paracetamol, gabapentin, and hydrocortisone	Resolved with reinsertion of spinal implants	Unlikely
Age 15 white female	Opana 5 mg one dose	Anemia, pupils unequal, vision blurred, & headache	Underwent left femur and tibial osteotomy surgery and intramedullary nailing, progressively worsening anemia after surgery, multiple opioids including a single dose of study drug, morphine, and oxycodone for post-operative pain, experienced double and blurred vision and headache, all resolved at initial discharge, worse after touching scopolamine patch (applied for nausea) presented with unequal pupil dilatation at hospital readmission, received blood transfusion for severe anemia	Enoxaparin, cefazolin, paracetamol, metoclopramide, prenatal vitamins, hydromorphone, ondansetron, hydromorphone, Sennoside, docusate, and bisacodyl	Resolved	Unlikely
Study EN3319-302						
Age 5 white female	0.05 mg/kg single dose	Neutropenia, Postoperative fever	Received oxymorphone oral liquid 1.2 mL single dose for pain post biopsy of abdominal mass, diagnosed with embryonal rhabdomyosarcoma, completed a week of chemotherapy, readmitted 9 days later for fever, urinary symptoms consistent with UTI, and neutropenia, which responded to antibiotics.	Coumadin (warfarin), oxycodone, OxyContin (oxycodone), Neupogen (filgrastim), Neurontin (gabapentin), and senna	Resolved with treatment	Unlikely
Age 11 white male	0.10 mg/kg single dose	Joint dislocation postoperative	Had medical history of slipped capital femoral epiphysis, and bilateral hip dislocation and femoral neck osteotomies, received oxymorphone oral liquid 6.4 mg single dose during recovery from bilateral hip dislocations and femoral neck osteotomies, had left hip dislocation detected by X-ray 5 days later.	calcium gluconate, cefazolin, acetaminophen, ondansetron, diazepam, docusate, morphine and oxycodone	Resolved with treatment	Unlikely
Age 7 white male	0.20 mg/kg 8 doses	Abdominal abscess	Presented with a ruptured appendix and multiple abdominal abscesses and underwent open appendectomy, new abdominal abscesses by CT 4 days later leading to prolonged hospitalization	oxymorphone oral liquid 4 mg q6 hours for 2 days	Resolved with treatment	Unlikely
Age 9 white male	0.20 mg/kg 3 doses	Wound dehiscence	Had rib cartilage harvest and stage 1 microtia repair, oxymorphone discontinued due to lethargy, wound dehiscence at follow-up visit 12 days later and had surgical repair.	oxymorphone oral liquid 5-8 mg q4 hours, 3 doses	Resolved with treatment	Unlikely

Source: Table 14.3.3 pp. 169-172 study report for Study EN3203-010 and Table 14.3.3. pp.123-126 study report for Study EN3319-302.

Discontinuation due to Adverse Events (AEs)

Cases of early discontinuation due to AEs are listed by the age group and dosage in the table below. Five cases of early discontinuation were reported in pediatric studies during the multiple-dose phase with two in the age group of greater than 12 to 17 years, two in the age group of 6 to 12 years, and one in the age group of 2 to less than 6 years.

Case Summary for Study Discontinuation due to AEs

Age Groups	**Age >12–17 years (n=58)**			**Age 6–≤12 years (n=29)**			**Age 2–<6 years (n=25)**			**Age 0–<2 years (n=7)**
Dose level	5 mg	10 mg	15 mg	0.05 mg/kg	0.1 mg/kg	0.2 mg/kg	0.05 mg/kg	0.1 mg/kg	0.2 mg/kg	0.05 mg/kg
Single dose	13	9	11	6	6	7	7	6	6	7
AE Dropouts										
Multiple dose	9	8	8	0	0	10	0	0	6	0
AE Dropouts	***1***		***1***			***2***			***1***	

Source: Individual study reports.

Case narratives for early discontinuation due to AEs were summarized in terms of exposure, type of AE, brief description of the events leading to early discontinuation, concomitant medication, outcome of AE, and the relationship of AE with the study drug as shown in the table below. Five pediatric early dropouts were due to CNS symptoms with two cases of sedation and one case each of tremor, somnolence, and lethargy. All pediatric cases resolved spontaneously and were considered to be probably related to the study drug based on the case narratives provided.

Case Summary for Study Discontinuation due to AEs

Patient	**Study drug**	**AE**	**Brief description**	**Concomitant medication**	**Outcome of AE**	**Related to study drug**
Study EN3203-010						
Age 16 white male	Opana 5 mg 3 doses	Sedation	Discontinued Opana 5 mg due to moderate sedation, other AEs: mild decrease in oxygen saturation, moderate hypertension, mild tachycardia , mild constipation next day, and mild urinary retention 2 days later	Fluticasone propionate, montelukast, loratadine, sertraline, midodrine, budesonide, salbutamol, cefazolin, paracetamol, Vicodin, Sennoside, fludrocortisone, bisacodyl	Resolved	Probably
Age 16 white male	Opana 15 mg 1-dose	Tremor	Discontinued Opana 15 mg due to moderate tremor, other AEs included mild pruritus, pyrexia, dizziness, and urinary retention,	Morphine, ibuprofen, ketorolac, ondansetron, docusate, paracetamol, oxycodone, famotidine hydromorphone, ,	Resolved	Probably
Study EN3319-302						
Age 9 black male	0.20 mg/kg 4-dose	Sedation	Discontinued oxymorphone oral liquid due to mild sedation		Resolved	Probably
Age 2 white male	0.20 mg/kg 1-dose	Somnolence	Discontinued oxymorphone oral liquid due to moderate somnolence		Resolved	Probably
Age 9 white male	0.20 mg/kg 3-dose	Lethargy	Discontinued oxymorphone oral liquid due to moderate lethargy		Resolved	Probably

Source: Table 14.3.3 pp. 174-175 study report for Study EN3203-010 and Table 14.3.3. pp. 127-129 study report for Study EN3319-302.

Treatment-emergent adverse events

Treatment-emergent AEs or TEAEs are summarized in various ways: by age group subtotals including both single-and multiple-dose phases and by single-dose versus multiple-dose across age groups. Dose response is then explored in detail by presenting TEAEs by dose level per treatment phase (single- and multiple-dose) for the age group of greater than 12 to 17 years in Study EN3203-010 and for the three age groups in Study EN3319-302.

Common TEAEs per age group (single-and multiple-dose phases combined) and per study phase across age groups are summarized in the table below. For the entire pediatric population, two thirds of patients reported AEs with about 60% in the single-dose phase and 80% in the multiple-dose phase. Individual AEs reported noticeably more in the multiple-dose than the single-dose phase included constipation, nausea, dizziness, urinary retention, oxygen saturation decreased, and anemia. The number of patients with AEs and reporting rates varied between the age groups with fewer patients studied in the younger age groups and fewer reported AEs in these groups. The most common AEs (≥5%) for the entire pediatric population included (in order of decreasing reporting frequency) nausea, pyrexia, constipation, vomiting, pruritus, and headache. The next most common AEs included five cases (4%) of each of the following: peripheral edema, oxygen saturation decreased, muscle spasms, dizziness, and urinary retention. The AEs were generally consistent with common post-operative and opioid-related findings.

Common TEAEs Per Age Group and Per Study Phase Across Age Group

Common AEs, N (%)	**By age group**				**By study phase**		
Subgroup	**>12-17**	**6-12**	**2-<6**	**0-<2**	**SD, all age**	**MD, all age**	**Total**
#patients in the subpopulation	N=58	N=29	N=25	N=7	N=78	N=41	N=119
#Patients with any AE	33 (56.9)	23 (79.3)	19 (76.0)	4 (57.1)	46 (59.0)	33 (80.5)	79 (66.4)
Blood and lymphatic system disorders							
Anemia	4 (6.9)	0	0	0	0	4 (9.8)	4 (3.4)
Gastrointestinal disorders							
Abdominal distension	2 (3.4)	0	2 (8.0)	0	2 (2.6)	2 (4.9)	4 (3.4)
Constipation	10 (17.2)	2 (6.9)	2 (8.0)	0	5 (6.4)	9 (22.0)	14 (11.8)
Nausea	11 (19.0)	6 (20.7)	1 (4.0)	0	7 (9.0)	11 (26.8)	18 (15.1)
Vomiting	5 (8.6)	5 (17.2)	2 (8.0)	1 (14.3)	6 (7.7)	7 (17.1)	13 (10.9)
General disorders and admin. site conditions							
Peripheral edema	0	0	3 (12.0)	2 (28.6)	4 (5.1)	1 (2.4)	5 (4.2)
Pyrexia	7 (12.1)	6 (20.7)	2 (8.0)	0	9 (11.5)	6 (14.6)	15 (12.6)
Injury, poisoning and procedural complications							
Postoperative fever	0	2 (6.9)	2 (8.0)	0	4 (5.1)	0	4 (3.4)
Procedural nausea	0	0	2 (8.0)	0	2 (2.6)	0	2 (1.7)
Procedural pain	0	1 (3.4)	2 (8.0)	0	3 (3.8)	0	3 (2.5)
Investigations	0	0	0	0	0	0	0
Oxygen saturation decreased	5 (8.6)	0	0	0	1 (1.3)	4 (9.8)	5 (4.2)
Musculoskeletal and connective tissue disorders							
Muscle spasms	3 (5.2)	2 (6.9)	0	0	3 (3.8)	2 (4.9)	5 (4.2)
Nervous system disorders							
Dizziness	5 (8.6)	0	0	0	1 (1.3)	4 (9.8)	5 (4.2)
Headache	4 (6.9)	2 (6.9)	0	0	0	6 (14.6)	6 (5.0)
Renal and urinary disorders							
Urinary retention	5 (8.6)	0	0	0	1 (1.3)	4 (9.8)	5 (4.2)
Skin and subcutaneous tissue disorders							
Pruritus	4 (6.9)	2 (6.9)	2 (8.0)	0	3 (3.8)	5 (12.2)	8 (6.7)

Source: the table below.

Common TEAEs Per Study Phase for Each Age Group

Common AEs, N (%)	Study EN3203-010		Study EN3319-302				
Age group	**>12-17 years**		**6-12 years**		**2-<6 years**		**0-<2 years**
Study phase	Single-dose	Multi-dose	Single-dose	Multi-dose	Single-dose	Multi-dose	Single-dose
#patients in the subpopulation	N=33	N=25	N=19	N=10	N=19	N=6	N=7
#Patients with any AE	14 (42.4%)	19 (76.0%)	13 (68.4)	10 (100.0)	15 (78.9)	4 (66.7)	4 (57.1)
Blood and lymphatic system disorders							
Anemia	0	4	0	0	0	0	0
Gastrointestinal disorders							
Abdominal distension	0	2	0	0	2 (10.5)	0	0
Constipation	2 (6.1%)	8 (32.0%)	1 (5.3)	1 (10.0)	2 (10.5)	0	0
Nausea	4 (12.1%)	7 (28.0%)	2 (10.5)	4 (40.0)	1 (5.3)	0	0
Vomiting	2 (6.1%)	3 (12.0%)	1 (5.3)	4 (40.0)	2 (10.5)	0	1 (14.3)
General disorders and admin. site conditions							
Peripheral edema	0	0	0	0	2 (10.5)	1 (16.7)	2 (28.6)
Pyrexia	4 (12.1%)	3 (12.0%)	4 (21.1)	2 (20.0)	1 (5.3)	1 (16.7)	0
Injury, poisoning and procedural complications							
Postoperative fever	0	0	2 (10.5)	0	2 (10.5)	0	0
Procedural nausea	0	0	0	0	2 (10.5)	0	0
Procedural pain	0	0	1 (5.3)	0	2 (10.5)	0	0
Investigations							
Oxygen saturation decreased	1 (3.0%)	4 (16.0%)	0	0	0	0	0
Musculoskeletal and connective tissue disorders							
Muscle spasms	1 (3.0%)	2 (8.0%)	2 (10.5)	0	0	0	0
Nervous system disorders							
Dizziness	1 (3.0%)	4 (16.0%)	0	0	0	0	0
Headache	0	4 (16.0%)	0	2 (20.0)	0	0	0
Renal and urinary disorders							
Urinary retention	1 (3.0%)	4 (16.0%)	0	0	0	0	0
Skin and subcutaneous tissue disorders							
Pruritus	1 (3.0%)	3 (12.0%)	1 (5.3)	1 (10.0)	1 (5.3)	1 (16.7)	0

Source: Table 15 on pages 53-54 of study report for Study EN3203-010 and Table 28 on pages 102-105 and Table 29 on pages 107-108 of study report for Study EN3319-302.

The next table summarizes common AEs defined as AEs reported in more than one patient from any of the dose groups during either the single-dose phase or the multiple-dose phase in Study EN3203-010 and is followed by a tabular summary of all AEs per dose group per study phase, which is presented as a reference.

In Study EN3203-010, which included the >12 to 17 years age group, more AEs were reported in the multiple-dose phase than the single-dose phase overall and in terms of the types of the individual AEs.

The most frequently reported individual AEs in single-dose phase included four cases of pyrexia (all at 15 mg dose) and four cases of nausea (one at 5 mg dose, two at 10 mg dose, and one at 15 mg dose). Other more frequently reported AEs included two cases of constipation (one at 5 mg dose and one at 15 mg dose) and two cases of vomiting (one at 5 mg dose and one at 10 mg dose).

In the multiple-dose phase, the most frequently reported individual AEs included eight cases of constipation (three at 5 mg dose, four at 10 mg dose, and one at 15 mg dose) and seven cases of nausea (four at 5 mg dose, two at 10 mg dose, and one at 15 mg dose). Other more frequently

reported AEs included four cases of each of the following: anemia (one at 5 mg dose and three at 15 mg dose), oxygen saturation decreased (two at 5 mg dose and two at 15 mg dose), dizziness (one at 5 mg dose, two at 10 mg dose, and one at 15 mg dose), headache (three at 5 mg dose and one at 15 mg dose), and urinary retention (one at 5 mg dose and three at 15 mg dose), and three cases of each of the following: vomiting (two at 5 mg dose and one at 15 mg dose) and pyrexia (one at 5 mg dose and two at 15 mg dose).

The findings were generally consistent with what would be expected postoperatively and with the known safety profile associated with opioid analgesics. The data did not reveal any trend to suggest a dose response; however, this evaluation was limited due to small sample sizes for the dose/age subgroup and the short treatment duration as well as the relatively small differences in dose levels studied.

Common AEs, More Than One report in Any Dose Group, Study EN3203-010

Study EN3203-010	**Single Dose of Oxymorphone IR**				**Multiple Dose of Oxymorphone IR**			
System Organ Class/Preferred Term	**5 mg (N=13)**	**10 mg (N=9)**	**15 mg (N=11)**	**Overall (N=33)**	**5 mg (N=9)**	**10 mg (N=8)**	**15 mg (N=8)**	**Overall (N=25)**
#Patients with any AE	3 (23.1%)	4 (44.4%)	7 (63.6%)	**14 (42.4%)**	8 (88.9%)	5 (62.5%)	6 (75.0%)	**19 (76.0%)**
Blood and lymphatic system disorders								
Anemia	0	0	0	0	1 (11.1%)	0	**3 (37.5%)**	4 (16.0%)
Gastrointestinal disorders								
Constipation	1 (7.7%)	0	1 (9.1%)	2 (6.1%)	**3 (33.3%)**	**4 (50.0%)**	1 (12.5%)	8 (32.0%)
Nausea	1 (7.7%)	**2 (22.2%)**	1 (9.1%)	4 (12.1%)	**4 (44.4%)**	**2 (25.0%)**	1 (12.5%)	7 (28.0%)
Vomiting	1 (7.7%)	1 (11.1%)	0	2 (6.1%)	**2 (22.2%)**	0	1 (12.5%)	3 (12.0%)
General disorders and administration site conditions								
Pyrexia	0	0	**4 (36.4%)**	4 (12.1%)	1 (11.1%)	0	**2 (25.0%)**	3 (12.0%)
Investigations								
Oxygen saturation decreased	1 (7.7%)	0	0	1 (3.0%)	**2 (22.2%)**	0	**2 (25.0%)**	**4 (16.0%)**
Musculoskeletal and connective tissue disorders								
Muscle spasms	1 (7.7%)	0	0	1 (3.0%)	0	**2 (25.0%)**	0	2 (8.0%)
Nervous system disorders								
Dizziness	1 (7.7%)	0	0	1 (3.0%)	1 (11.1%)	**2 (25.0%)**	1 (12.5%)	4 (16.0%)
Headache	0	0	0	0	**3 (33.3%)**	0	1 (12.5%)	4 (16.0%)
Renal and urinary disorders								
Urinary retention	0	0	1 (9.1%)	1 (3.0%)	1 (11.1%)	0	**3 (37.5%)**	4 (16.0%)

Source: the table below.

TEAEs Reported in ≥5% in Either Treatment Phase, Study EN3203-010

Study EN3203-010	Single Dose of Oxymorphone IR				Multiple Dose of Oxymorphone IR			
System Organ Class/Preferred Term	5 mg (N=13)	10 mg (N=9)	15 mg (N=11)	Overall (N=33)	5 mg (N=9)	10 mg (N=8)	15 mg (N=8)	Overall (N=25)
#Patients with any AE	3 (23.1%)	4 (44.4%)	7 (63.6%)	14 (42.4%)	8 (88.9%)	5 (62.5%)	6 (75.0%)	19 (76.0%)
Blood and lymphatic system disorders	0	0	0	0	1 (11.1%)	0	3 (37.5%)	4 (16.0%)
Anemia	0	0	0	0	1 (11.1%)	0	**3 (37.5%)**	4 (16.0%)
Cardiac disorders	1 (7.7%)	0	0	1 (3.0%)	1 (11.1%)	1 (12.5%)	0	2 (8.0%)
Tachycardia	1 (7.7%)	0	0	1 (3.0%)	1 (11.1%)	1 (12.5%)	0	2 (8.0%)
Gastrointestinal disorders	2 (15.4%)	2 (22.2%)	1 (9.1%)	5 (15.2%)	5 (55.6%)	4 (50.0%)	3 (37.5%)	12 (48.0%)
Abdominal distension	0	0	0	0	0	1 (12.5%)	1 (12.5%)	2 (8.0%)
Constipation	1 (7.7%)	0	1 (9.1%)	2 (6.1%)	**3 (33.3%)**	**4 (50.0%)**	1 (12.5%)	8 (32.0%)
Nausea	1 (7.7%)	**2 (22.2%)**	1 (9.1%)	4 (12.1%)	**4 (44.4%)**	**2 (25.0%)**	1 (12.5%)	7 (28.0%)
Vomiting	1 (7.7%)	1 (11.1%)	0	2 (6.1%)	**2 (22.2%)**	0	1 (12.5%)	3 (12.0%)
General disorders and administration site conditions	1 (7.7%)	0	4 (36.4%)	5 (15.2%)	2 (22.2%)	0	2 (25.0%)	4 (16.0%)
Pyrexia	0	0	**4 (36.4%)**	4 (12.1%)	1 (11.1%)	0	**2 (25.0%)**	3 (12.0%)
Investigations	1 (7.7%)	0	0	1 (3.0%)	2 (22.2%)	0	2 (25.0%)	4 (16.0%)
Oxygen saturation decreased	1 (7.7%)	0	0	1 (3.0%)	**2 (22.2%)**	0	**2 (25.0%)**	**4 (16.0%)**
Musculoskeletal and connective tissue disorders	1 (7.7%)	0	0	1 (3.0%)	0	2 (25.0%)	1 (12.5%)	3 (12.0%)
Muscle spasms	1 (7.7%)	0	0	1 (3.0%)	0	**2 (25.0%)**	0	2 (8.0%)
Nervous system disorders	2 (15.4%)	2 (22.2%)	0	4 (12.1%)	4 (44.4%)	2 (25.0%)	2 (25.0%)	8 (32.0%)
Dizziness	1 (7.7%)	0	0	1 (3.0%)	1 (11.1%)	**2 (25.0%)**	1 (12.5%)	4 (16.0%)
Headache	0	0	0	0	**3 (33.3%)**	0	1 (12.5%)	4 (16.0%)
Hypoesthesia	1 (7.7%)	1 (11.1%)	0	2 (6.1%)	0	0	0	0
Sedation	0	0	0	0	1 (11.1%)	0	1 (12.5%)	2 (8.0%)
Psychiatric disorders	0	0	0	0	1 (11.1%)	1 (12.5%)	0	2 (8.0%)
Anxiety	0	0	0	0	1 (11.1%)	1 (12.5%)	0	2 (8.0%)
Renal and urinary disorders	0	0	1 (9.1%)	1 (3.0%)	2 (22.2%)	0	3 (37.5%)	5 (20.0%)
Urinary retention	0	0	1 (9.1%)	1 (3.0%)	1 (11.1%)	0	**3 (37.5%)**	4 (16.0%)
Respiratory, thoracic and mediastinal disorders	1 (7.7%)	1 (11.1%)	1 (9.1%)	3 (9.1%)	1 (11.1%)	2 (25.0%)	1 (12.5%)	4 (16.0%)
Pleural effusion	0	0	0	0	0	1 (12.5%)	1 (12.5%)	2 (8.0%)
Skin and subcutaneous tissue disorders	1 (7.7%)	0	1 (9.1%)	2 (6.1%)	2 (22.2%)	1 (12.5%)	1 (12.5%)	4 (16.0%)
Pruritus	1 (7.7%)	0	0	1 (3.0%)	1 (11.1%)	1 (12.5%)	1 (12.5%)	3 (12.0%)

Source: Table 15 on pages 53-54 of study report for Study EN3203-010.

The next table summarizes common AEs defined as AEs reported in more than one patient from any of the dose group during either the single-dose phase or the multiple-dose phase in each age group in Study EN3319-302 and is followed by a tabular summary of all AEs per dose group per study phase per age group, which is presented as a reference.

In Study EN3319-302, pediatric subjects in all three age groups received a single dose at three dose levels of 0.05, 0.1, and 0.2 mg/kg. Only the 0.2 mg/kg was studied in the multiple-dose phase.

For the age group of 6 to 12 years, more frequently reported individual AEs included four cases of pyrexia (three at 0.1 mg/kg dose and one at 0.2 mg/kg dose) and two cases of each of the following nausea (one at 0.1 mg/kg dose and one at 0.2 mg/kg dose), postoperative fever (one at 0.05 mg/kg dose and one at 0.1 mg/kg dose), and muscle spasms (both at 0.1 mg/kg dose) in the single-dose phase. More frequently reported individual AEs during the multiple-dose phase included four cases of nausea, four cases of vomiting, two cases of pyrexia, and two cases of headache.

For the age group of 2 to less than 6 years, more frequently reported individual AEs in the single-dose phase included two cases of each of the following: abdominal distension, peripheral edema, postoperative fever, procedural nausea, and procedural pain at 0.05 mg/kg dose level and constipation and vomiting at 0.1 mg/kg dose level. None of the AEs was reported by more than one patient during the multiple-dose phase.

More frequently reported individual AEs in the age group of 0 to less than 2 years were two cases of peripheral edema.

These more frequently reported individual AEs were mostly related to postoperative and gastrointestinal symptoms. Dose response was not studied in the multiple-dose phase and a single dose of the study drug is not expected to show any dose response in such small samples of 6-7 patients per dose group.

Common AEs, More Than One report in Any Dose Group, Study EN3319-302

EN3319-302	**6 to ≤12 yrs**				**2 to <6 yrs**				**0 to <2 yrs**
	Single dose			**Multidose**	**Single dose**			**Multidose**	**Single dose**
System Organ Class/Preferred Term	**.05mg/kg (N=6)**	**0.1mg/kg (N=6)**	**0.2mg/kg (N=7)**	**0.2 mg/kg (N=10)**	**.05mg/kg (N=7)**	**0.1mg/kg (N=6)**	**0.2mg/kg (N=6)**	**0.2 mg/kg (N=6)**	**.05mg/kg (N=7)**
#Patients with any AE	5 (83.3)	4 (66.7)	**4 (57.1)**	**10 (100.0)**	7 (100.0)	5 (83.3)	**3 (50.0)**	**4 (66.7)**	4 (57.1)
Gastrointestinal disorders									
Abdominal distension	0	0	0	0	**2 (28.6)**	0	0	0	0
Constipation	0	1 (16.7)	0	1 (10.0)	0	**2 (33.3)**	0	0	0
Nausea	0	1 (16.7)	1 (14.3)	**4 (40.0)**	0	0	1 (16.7)	0	0
Vomiting	0	0	1 (14.3)	**4 (40.0)**	0	**2 (33.3)**	0	0	1 (14.3)
General disorders and admin. site conditions									
Peripheral edema	0	0	0	0	**2 (28.6)**	0	0	1 (16.7)	**2 (28.6)**
Pyrexia	0	**3 (50.0)**	1 (14.3)	**2 (20.0)**	0	1 (16.7)	0	1 (16.7)	0
Injury, poisoning and procedural complications									
Postoperative fever	1 (16.7)	1 (16.7)	0	0	**2 (28.6)**	0	0	0	0
Procedural nausea	0	0	0	0	**2 (28.6)**	0	0	0	0
Procedural pain	1 (16.7)	0	0	0	**2 (28.6)**	0	0	0	0
Musculoskeletal and connective tissue disorders									
Muscle spasms	0	**2 (33.3)**	0	0	0	0	0	0	0
Nervous system disorders									
Headache	0	0	0	**2 (20.0)**	0	0	0	0	0

Source: the table below.

TEAEs for Study EN3319-302

Study EN3319-302	6 to ≤12 yrs				2 to <6 yrs				0 to <2 yrs
	Single dose			Multidose	Single dose			Multidose	Single dose
System Organ Class/Preferred Term	.05mg/kg (N=6)	0.1mg/kg (N=6)	0.2mg/kg (N=7)	0.2 mg/kg (N=10)	.05mg/kg (N=7)	0.1mg/kg (N=6)	0.2mg/kg (N=6)	0.2 mg/kg (N=6)	.05mg/kg (N=7)
#Patients with any AE	5 (83.3)	4 (66.7)	4 (57.1)	10 (100.0)	7 (100.0)	5 (83.3)	3 (50.0)	4 (66.7)	4 (57.1)
Blood and lymphatic system disorders	0	0	0	0	1 (14.3)	0	0	1 (16.7)	0
Coagulopathy	0	0	0	0	0	0	0	1 (16.7)	0
Neutropenia	0	0	0	0	1 (14.3)	0	0	0	0
Cardiac disorders	0	0	0	0	1 (14.3)	1 (16.7)	0	0	0
Bradycardia	0	0	0	0	0	1 (16.7)	0	0	0
Sinus arrhythmia	0	0	0	0	0	1 (16.7)	0	0	0
Tachycardia	0	0	0	0	1 (14.3)	0	0	0	0
Gastrointestinal disorders	0	2 (33.3)	1 (14.3)	8 (80.0)	2 (28.6)	2 (33.3)	1 (16.7)	0	1 (14.3)
Abdominal distension	0	0	0	0	**2 (28.6)**	0	0	0	0
Constipation	0	1 (16.7)	0	1 (10.0)	0	**2 (33.3)**	0	0	0
Diarrhea	0	1 (16.7)	0	1 (10.0)	0	0	0	0	0
Ileus paralytic	0	0	0	1 (10.0)	0	0	0	0	0
Nausea	0	1 (16.7)	1 (14.3)	**4 (40.0)**	0	0	1 (16.7)	0	0
Vomiting	0	0	1 (14.3)	**4 (40.0)**	0	**2 (33.3)**	0	0	1 (14.3)
General disorders and admin. site conditions	0	3 (50.0)	1 (14.3)	4 (40.0)	3 (42.9)	3 (50.0)	0	2 (33.3)	3 (42.9)
Face edema	0	0	0	0	0	1 (16.7)	0	0	0
Fatigue	0	0	0	1 (10.0)	0	0	0	0	
General edema	0	0	0	1 (10.0)	1 (14.3)	0	0	0	0
Localized edema	0	0	0	0	0	0	0	0	1 (14.3)
Peripheral Edema	0	0	0	0	**2 (28.6)**	0	0	1 (16.7)	**2 (28.6)**
Peripheral swelling	0	1 (16.7)	0	0	1 (14.3)	1 (16.7)	0	0	0
Pyrexia	0	**3 (50.0)**	1 (14.3)	**2 (20.0)**	0	1 (16.7)	0	1 (16.7)	0
Infections and infestations	0	0	0	1 (10.0)	0	0	0	0	0
Abdominal abscess	0	0	0	1 (10.0)	0	0	0	0	
Injury, poisoning and procedural complications	5 (83.3)	1 (16.7)	0	2 (20.0)	4 (57.1)	0	0	0	0
Fall	1 (16.7)	0	0	0	0	0	0	0	0
Infusion site edema	0	0	0	1 (10.0)	0	0	0	0	
Joint dislocation	0	1 (16.7)	0	0	0	0	0	0	0
Postoperative fever	1 (16.7)	1 (16.7)	0	0	**2 (28.6)**	0	0	0	0
Procedural anxiety	1 (16.7)	0	0	0	0	0	0	0	0
Procedural nausea	0	0	0	0	**2 (28.6)**	0	0	0	0
Procedural pain	1 (16.7)	0	0	0	**2 (28.6)**	0	0	0	0
Procedural vomiting	1 (16.7)	0	0	0	0	0	0	0	0
Wound dehiscence	0	0	0	1 (10.0)	0	0	0	0	0
Investigations	0	0	0	1 (10.0)	1 (14.3)	0	0	0	1 (14.3)
ALT increased	0	0	0	0	0	0	0	0	1 (14.3)
AST increased	0	0	0	1 (10.0)	0	0	0	0	1 (14.3)
Clostridium test +	0	0	0	0	1 (14.3)	0	0	0	0
Hematocrit decreased	0	0	0	0	0	0	0	0	1 (14.3)
Hemoglobin decreased	0	0	0	0	0	0	0	0	1 (14.3)
RBC count decreased	0	0	0	0	0	0	0	0	1 (14.3)
WBC count decreased	0	0	0	0	0	0	0	0	1 (14.3)
Musculoskeletal and connective tissue disorders	0	2 (33.3)	0	1 (10.0)	0	1 (16.7)	0	0	0
Arthralgia	0	0	0	1 (10.0)	0	0	0	0	0
Foot deformity	0	0	0	0	0	1 (16.7)	0	0	0
Muscle spasms	0	**2 (33.3)**	0	0	0	0	0	0	0
Nervous system disorders	0	0	0	3 (30.0)	0	1 (16.7)	0	1 (16.7)	0
Cerebrospinal fluid leakage	0	0	0	0	0	1 (16.7)	0	0	0

Headache	0	0	0	**2 (20.0)**	0	0	0	0	0
Lethargy	0	0	0	1 (10.0)	0	0	0	0	0
Sedation	0	0	0	1 (10.0)	0	0	0	0	0
Somnolence	0	0	0	0	0	0	0	1 (16.7)	0
Vision blurred	0	0	0	1 (10.0)	0	0	0	0	0
Product issues	0	0	1 (14.3)	0	0	0	0	0	0
Device dislocation	0	0	1 (14.3)	0	0	0	0	0	0
Psychiatric disorders	0	0	1 (14.3)	0	0	0	0	0	0
Anxiety	0	0	1 (14.3)	0	0	0	0	0	0
Renal and urinary disorders	0	0	0	0	0	0	0	1 (16.7)	0
Enuresis	0	0	0	0	0	0	0	1 (16.7)	0
Reproductive system and breast disorders	0	0	0	0	1 (14.3)	0	0	0	0
Edema genital	0	0	0	0	1 (14.3)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (10.0)	0	0	1 (16.7)	0	0
Atelectasis	0	0	0	1 (10.0)	0	0	0	0	0
Hypoxia	0	0	0	0	0	0	1 (16.7)	0	0
Pleural effusion	0	0	0	1 (10.0)	0	0	0	0	0
Skin and subcutaneous tissue disorders	1 (16.7)	1 (16.7)	0	1 (10.0)	1 (14.3)	3 (50.0)	1 (16.7)	1 (16.7)	0
Pruritus	1 (16.7)	0	0	1 (10.0)	0	1 (16.7)	0	1 (16.7)	0
Blood blister	0	0	0	0	1 (14.3)	0	0	0	0
Dermatitis contact	0	1 (16.7)	0	0	0	0	0	0	0
Erythema	0	0	0	0	0	1 (16.7)	0	0	0
Rash	0	0	0	0	0	0	1 (16.7)	0	0
Swelling face	0	0	0	0	0	1 (16.7)	0	0	0
Surgical and medical procedures	0	1 (16.7)	0	1 (10.0)	0	0	0	0	0
Central venous catheterization	0	0	0	1 (10.0)	0	0	0	0	0
Incisional drainage	0	1 (16.7)	0	0	0	0	0	0	0
Vascular disorders	0	0	1 (14.3)	0	0	0	0	0	0
Hypotension	0	0	1 (14.3)	0	0	0	0	0	0

Source: Table 28 pp. 102-105 and Table 29, pp. 107-108 of study report for Study EN3319-302.

Laboratory findings

Across the two studies, clinically significant shifts in laboratory results were reported in some patients, including decreases in hematocrit, hemoglobin, RBC, lymphocytes, albumin, protein, calcium, and bicarbonate and increase in glucose. However, no concerning trends could be identified and the changes in laboratory values observed are generally expected in the population studied.

Clinical Safety Summary

The pediatric safety database supporting the current pediatric supplement for Opana tablets consists of 119 pediatric patients who received oxymorphone treatment including 58 in the greater than 12 to 17 years of age group exposed to the tablet formulation and 61 in the 2 to 12 years of age group exposed to the oral solution formulation. Sixteen patients in the greater than 12 to 17 years of age group and 14 patients in the 2 to 12 years of age group were exposed to more than one dose. The maximum exposures consisted of exposure to 8-12 doses of the 15 mg tablet by five patients in the greater than 12 to 17 years age group and 8-12 doses of 0.2 mg/kg solution by seven patients in the 2 to 12 years age group.

Safety findings included no cases of death, seven cases of serious AEs, and five cases of early discontinuation due to AEs. All SAEs were considered unlikely to be related to the study drug and all AE-related early dropouts were due to CNS symptoms such as sedation, tremor, somnolence, and lethargy based on analyses of case narratives.

Treatment-emergent AEs (TEAEs) pooled across studies revealed that approximately two thirds (66%) of pediatric patients experienced AEs, and more AEs were reported with multiple-doses than with single-doses (80% versus 60%, respectively). The most commonly reported AEs (≥5%) included nausea, pyrexia, constipation, vomiting, and headache.

The reported safety findings from the database were generally consistent with post-operative experiences and with the known safety profile of opioid analgesics. However, the overall data submitted raise concerns related to the safety of oxymorphone in pediatric populations, as well as for efficacy.

Specifically, the clinical pharmacology review noted that two of 24 subjects (~8%) in Study EN3203-010 (study in greater than 12 to 17 years age group) had substantially higher oxymorphone exposure levels and were considered outliers in the pharmacokinetic analysis. The details for these subjects are listed below:

- Subject EN3203-010-0004-1002 was a 13-year-old female that received a single 5-mg dose of oxymorphone and completed the study. No adverse events were reported for this subject. This subject's pain intensity score on a 100-mm visual analog scale (VAS) went from 50 mm at baseline to 20 mm at the 6-hour post-dose/time of rescue time point. Her pain intensity scores generally trended down over the post-dose assessment period.

- Subject EN3203-010-0017-1002 was a 14-year-old female that received a single 15-mg dose of oxymorphone. This subject had three reported adverse events, including pruritus, fever, and asthma exacerbation; although, none of these were reported as serious or resulted in discontinuation. However, this subject did discontinue the study due to lack of efficacy. This subject's pain intensity score on a 100-mm visual analog scale (VAS) went from 62 mm at baseline to 52 mm at the 6-hour post-dose/time of rescue time point. Her pain intensity scores were variable over the post-dose assessment period.

Although these subjects may be outliers and did not experience significant safety concerns associated with their substantially higher oxymorphone exposure levels in the context of the study, the fact that nearly 10% of the population has substantially higher exposures is a potential safety issue.

Furthermore, although the submitted studies were open-label and were not designed to adequately evaluate efficacy, the fact that a substantial number of patients withdrew from the study due to lack of efficacy, including the outlier patient noted above that had higher exposures with the single 15-mg dose, certainly questions the efficacy of oxymorphone in the pediatric population.

Applicant's Proposed Labeling

See Appendix for the Applicant's proposed labeling.

Refer to guidance for industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling*, available at https://www.fda.gov/media/84949/download, for information regarding inclusion of pediatric information in labeling.

Appendix
Proposed Draft Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OPANA® safely and effectively. See full prescribing information for OPANA®.

OPANA® (oxymorphone hydrochloride) Tablets, for Oral use CII
Initial U.S. Approval: 1959

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.

- **OPANA exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)**
- **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. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.3)**
- **Accidental ingestion of OPANA, especially by children, can result in a fatal overdose of oxymorphone. (5.3)**
- **Prolonged use of OPANA 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 OPANA because co-ingestion can result in fatal plasma oxymorphone levels. (5.5)**
- **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. (5.5, 7)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	09/2018
Warnings and Precautions (5.2)	09/2018

----------INDICATIONS AND USAGE----------

OPANA is an opioid agonist indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

Limitations of Use (1)
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve OPANA for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

----------DOSAGE AND ADMINISTRATION----------

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.2)
- Initiate treatment with 10 to 20 mg orally every four to six hours.
- OPANA should be taken on an empty stomach, at least one hour prior to or two hours after eating. (2.1)
- Conversion to OPANA: Follow recommendations for conversion from other opioids or parenteral oxymorphone. (2.2)
- Do not stop OPANA abruptly in a physically dependent patient. (2.8)
- Mild Hepatic Impairment: Initiate treatment with 5 mg and titrate slowly. Monitor for signs of respiratory and central nervous system depression. (2.3)
- Renal Impairment: Initiate treatment with 5 mg and titrate slowly. Monitor for signs of respiratory and central nervous system depression. (2.4)
- Geriatric Patients: Initiate dosing with 5 mg, titrate slowly, and monitor for signs of respiratory and central nervous system depression. (2.5)
- CNS Depressants: Initiate treatment with 1/3 to 1/2 the recommended starting dose, consider using a lower dosage of the concomitant CNS depressant, and monitor closely. (2.6, 5.6, 7)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 5 mg and 10 mg. (3)

----------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 OPANA (4)
- Moderate or severe hepatic impairment (4)

----------WARNINGS AND PRECAUTIONS----------

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.3)
- Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions: If symptoms occur, stop administration immediately, discontinue permanently, and do not rechallenge with any oxymorphone formulation. (5.7)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of OPANA in patients with circulatory shock. (5.9)
- 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 OPANA in patients with impaired consciousness or coma. (5.10)

----------ADVERSE REACTIONS----------

Adverse reactions (≥ 2% of patients): Nausea, pyrexia, somnolence, vomiting, pruritus, headache, dizziness, constipation, and confusion. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Endo Pharmaceuticals Inc. at 1-800-462-3636 or FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue OPANA if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with OPANA because they may reduce analgesic effect of OPANA 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)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: ~~09~~XX/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

***Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

Addiction, Abuse, and Misuse

OPANA 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, 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 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**

- **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 OPANA. Monitor for respiratory depression, especially during initiation of OPANA or following a dose increase [***see Warnings and Precautions (5.3)***]**.**

Accidental Ingestion

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

Neonatal Opioid Withdrawal Syndrome

Prolonged use of OPANA 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)***]**.**

Interaction with Alcohol

Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking OPANA. The co-ingestion of alcohol with OPANA may result in increased plasma levels and a potentially fatal overdose of oxymorphone [***see Warnings and Precautions (5.5)***]**.**

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 (5.5), Drug Interactions (7)***]**.**

- **Reserve concomitant prescribing of OPANA 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.**

1 INDICATIONS AND USAGE

OPANA is indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses [*see Warnings and Precautions (5.1)*], reserve OPANA for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*].

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [*see Warnings and Precautions (5.1)*].

Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with OPANA and adjust the dosage accordingly [*see Warnings and Precautions (5.3)*].

OPANA should be administered on an empty stomach, at least one hour prior to or two hours after eating [*see Clinical Pharmacology (12.3)*].

To avoid medication errors, prescribers and pharmacists must be aware that oxymorphone is available as both immediate-release 5 mg and 10 mg tablets and extended-release 5 mg and 10 mg tablets [*see Dosage Forms and Strengths (3)*].

2.2 Initial Dosage

Use of OPANA as the first Opioid Analgesic

Initiate treatment with OPANA in a dosing range of 10 to 20 mg every 4 to 6 hours as needed for pain.

Do not initiate treatment with doses higher than 20 mg because of the potential serious adverse reactions [*see Clinical Studies (14.1)*].

Conversion from Other Opioids to OPANA

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of OPANA. It is safer to underestimate a patient’s 24-hour OPANA dosage than to overestimate the 24-hour OPANA dosage and manage an adverse reaction due to overdose.

For conversion from other opioids to OPANA, physicians and other healthcare professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate. In general, it is safest to start OPANA therapy by administering half of the calculated total daily dose of OPANA in 4 to 6 equally divided doses, every 4-6 hours. The initial dose of OPANA can be gradually adjusted until adequate pain relief and acceptable side effects have been achieved.

Conversion from Parenteral Oxymorphone to OPANA

Given OPANA's absolute oral bioavailability of approximately 10%, patients receiving parenteral oxymorphone may be converted to OPANA by administering 10 times the patient's total daily parenteral oxymorphone dose as OPANA, in four or six equally divided doses (e.g., [IV dose x 10] divided by 4 or 6). For example, approximately 10 mg of OPANA four times daily may be required to provide pain relief equivalent to a total daily IM dose of 4 mg oxymorphone. Due to patient variability with regard to opioid analgesic response, upon conversion patients should be closely monitored to ensure adequate analgesia and to minimize side effects.

Conversion from OPANA to Extended-Release Oxymorphone

The relative bioavailability of OPANA compared to extended-release oxymorphone is unknown, so conversion to extended-release tablets must be accompanied by close observation for signs of excessive sedation and respiratory depression.

2.3 Dosage Modifications in Patients with Mild Hepatic Impairment

OPANA is contraindicated in patients with moderate or severe hepatic impairment.

Use OPANA with caution in patients with mild hepatic impairment, starting with the lowest dose (e.g., 5 mg) and titrating slowly while carefully monitoring for signs of respiratory and central nervous system depression [*see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*].

2.4 Dosage Modifications in Patients with Renal Impairment

Use OPANA with caution in patients with creatinine clearance rates less than 50 mL/min~~,~~, starting with the lowest dose (e.g., 5 mg) and titrating slowly while carefully monitoring for signs of respiratory and central nervous system depression [*see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*].

2.5 Dosage Modifications in Geriatric Patients

Exercise caution in the selection of the starting dose of OPANA for an elderly patient by starting with the lowest dose (e.g., 5 mg) and titrate slowly while carefully monitoring for signs of respiratory and central nervous system depression [*see Use in Specific Populations (8.5*)].

2.6 Dosage Modifications with Concomitant Use with Central Nervous System Depressants

OPANA, like all opioid analgesics, should be started at one-third to one-half of the usual dose in patients who are concurrently receiving other central nervous system (CNS) depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol, because respiratory depression, hypotension and profound sedation, coma or death may result [*see Warnings and Precautions (5.5) and Drug Interactions (7)*]. When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced.

2.7 Titration and Maintenance of Therapy

Individually titrate OPANA to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OPANA to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [*see Warnings and Precautions (5.1)*]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the OPANA dosage. If unacceptable opioid-related adverse reactions are observed,

consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.8 Discontinuation of OPANA

When a patient who has been taking OPANA regularly and may be physically dependent no longer requires therapy with OPANA, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue OPANA in a physically-dependent patient [*see Warnings and Precautions (5.13), Drug Abuse and Dependence (9.2, 9.3)*].

3 DOSAGE FORMS AND STRENGTHS

Tablets 5 mg: blue, round, convex tablet debossed with E612 over 5 on one side and plain on the other.

Tablets 10 mg: red, round, convex tablet debossed with E613 over 10 on one side and plain on the other.

4 CONTRAINDICATIONS

OPANA is contraindicated in patients with:

- Significant respiratory depression [*see Warnings and Precautions (5.3)*]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [*see Warnings and Precautions (5.6)*]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [*see Warnings and Precautions (5.11)*]
- Hypersensitivity to oxymorphone (e.g., anaphylaxis, angioedema) or [*see Warnings and Precautions (5.7), Adverse Reactions (6)*]
- Moderate or severe hepatic impairment [*see Warnings and Precautions (5.15)*].

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

OPANA contains oxymorphone, a Schedule II controlled substance. As an opioid, OPANA exposes users to the risks of addiction, abuse, and misuse [*see Drug Abuse and Dependence (9)*].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OPANA. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing OPANA, and monitor all patients receiving OPANA 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 OPANA, but use in such patients necessitates intensive counseling about the risks and proper use of OPANA along with intensive monitoring for signs of addiction, abuse, and misuse.

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. 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 [*see Patient Counseling Information (17)*]. 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.

5.2 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 offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

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 www.fda.gov/OpioidAnalgesicREMSBlueprint.

5.3 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, 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 [*see Overdosage (10)*]. 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, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of OPANA.

To reduce the risk of respiratory depression, proper dosing and titration of OPANA are essential [*see Dosage and Administration (2)*]. Overestimating the OPANA 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 OPANA, especially by children, can result in respiratory depression and death due to an overdose of oxymorphone.

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of OPANA 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 [*see Use in Specific Populations (8.1), Patient Counseling Information (17)*].

5.5 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 therapy. The co-ingestion of alcohol with OPANA may result in increased plasma levels and a potentially fatal overdose of oxymorphone [*see Clinical Pharmacology (12.3)*].

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of OPANA with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine 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.

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 [*see Drug Interactions (7)*].

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 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 [*see Drug Interactions (7), Patient Counseling Information (17)*].

5.6 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of OPANA 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-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 [*see Warnings and Precautions (5.3)*].

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 [*see Warnings and Precautions (8.5)*].

Monitor such patients closely, particularly when initiating and titrating OPANA and when OPANA is given concomitantly with other drugs that depress respiration [*see Warnings and Precautions (5.3)*]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.7 Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions

Potentially life-threatening hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients treated with OPANA 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 immediately, discontinue OPANA 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 [*see Patient Counseling Information (17)*].

5.8 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.

5.9 Severe Hypotension

OPANA may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is 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) [*see Warnings and Precautions (5.5) and Drug Interactions (7)*]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of OPANA. In patients with circulatory shock, OPANA may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of OPANA in patients with circulatory shock.

5.10 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), OPANA may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with OPANA.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of OPANA in patients with impaired consciousness or coma.

5.11 Risks of Use in Patients with Gastrointestinal Conditions

OPANA is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The oxymorphone in OPANA may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.12 Increased Risk of Seizures in Patients with Seizure Disorders

The oxymorphone in OPANA 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 OPANA therapy.

5.13 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 OPANA. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms [*see Drug Interactions (7)*].

When discontinuing OPANA in a physically-dependent patient, gradually taper the dosage [*see Dosage and Administration (2.8)*]. Do not abruptly discontinue OPANA in these patients [*see Drug Abuse and Dependence (9.3)*].

5.14 Risks of Driving and Operating Machinery

OPANA 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 and know how they will react to the medication.

5.15 Hepatic Impairment

A study of extended-release oxymorphone tablets in patients with hepatic disease indicated greater plasma concentrations than in those with normal hepatic function [*see Clinical Pharmacology (12.3)*]. Use OPANA with caution in patients with mild impairment, starting with the lowest dose and titrating slowly while carefully monitoring for side effects [*see Dosage and Administration (2.2, 2.3)*]. OPANA is contraindicated in patients with moderate or severe hepatic impairment.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse [*see Warnings and Precautions (5.1)*]
- Life-Threatening Respiratory Depression [*see Warnings and Precautions (5.3)*]
- Neonatal Opioid Withdrawal Syndrome [*see Warnings and Precautions (5.4)*]
- Interactions with Benzodiazepines and Other CNS Depressants [*see Warnings and Precautions (5.5)*]
- Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions [*see Warnings and Precautions (5.7)*]
- Adrenal Insufficiency [*see Warnings and Precautions (5.8)*]
- Severe Hypotension [*see Warnings and Precautions (5.9)*]
- Gastrointestinal Adverse Reactions [*see Warnings and Precautions (5.11)*]
- Seizures [*see Warnings and Precautions (5.12)*]
- Withdrawal [*see Warnings and Precautions (5.13)*]

6.1 Clinical Trials Experience

Adult Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 591 patients were treated with OPANA in controlled clinical trials. The clinical trials consisted of patients with acute ~~post-operative~~postoperative pain (n=557) and cancer pain (n=34) trials.

The following table lists adverse reactions that were reported in at least 2% of patients receiving OPANA in placebo-controlled trials (acute ~~post-operative~~postoperative pain (N=557~~)).~~).

Table 1: Adverse Reactions Reported in Placebo-Controlled Trials		
MedDRA Preferred Term	**OPANA (N=557)**	**Placebo (N=270)**
Nausea	19%	12%
Pyrexia	14%	8%
Somnolence	9%	2%
Vomiting	9%	7%
Pruritus	8%	4%
Headache	7%	4%
Dizziness (Excluding Vertigo)	7%	2%
Constipation	4%	1%
Confusion	3%	<1%

The **common** (≥1% - <10%) adverse drug reactions reported at least once by patients treated with OPANA in the clinical trials organized by MedDRA's (Medical Dictionary for Regulatory Activities) System Organ Class were and not represented in Table 1:

Cardiac disorders: tachycardia

Gastrointestinal disorders: dry mouth, abdominal distention, and flatulence

General disorders and administration site conditions: sweating increased

Nervous system disorders: anxiety and sedation

Respiratory, thoracic and mediastinal disorders: hypoxia

Vascular disorders: hypotension

Other less common adverse reactions known with opioid treatment that were seen <1% in the OPANA trials includes the following:

Abdominal pain, ileus, diarrhea, agitation, disorientation, restlessness, feeling jittery, hypersensitivity, allergic reactions, bradycardia, central nervous system depression, depressed level of consciousness, lethargy, mental impairment, mental status changes, fatigue, depression, clamminess, flushing, hot flashes, dehydration, dermatitis, dyspepsia, dysphoria, edema, euphoric mood, hallucination, hypertension, insomnia, miosis, nervousness, palpitation, postural hypotension, syncope, dyspnea, respiratory depression, respiratory distress, respiratory rate decreased, oxygen saturation decreased, difficult micturition, urinary retention, urticaria, vision blurred, visual disturbances, weakness, appetite decreased, and weight decreased.

Clinical Trial Experience in Pediatric Patients 2 Years and Older

The safety of oxymorphone HCl was evaluated in two open-label trials with 54 patients 2 to ≤12 years of age and 58 patients >12 to 17 years of age. Table 2 includes a summary of the incidence of treatment emergent adverse events reported in ≥ 5% of patients aged 2 to ≤12 years. Table 3 includes a summary of the incidence of treatment emergent adverse events reported in ≥ 5% of patients aged >12 to 17 years.

Table 2: Incidence of Treatment Emergent Adverse Events in ≥ 5% of Patients Aged 2 to ≤12 Years

Preferred Term	2 to ≤12 years (N=54) n (%)
Pyrexia	8 (14.8)
Nausea	7 (13.0)
Vomiting	7 (13.0)
Constipation	4 (7.4)
Postoperative fever	4 (7.4)
Pruritus	4 (7.4)
Edema peripheral	3 (5.6)
Peripheral swelling	3 (5.6)
Procedural pain	3 (5.6)

Table 3: Incidence of Treatment Emergent Adverse Events in ≥ 5% of Patients Aged >12 to 17 Years

Preferred Term	>12 to 17 years (N=58) n (%)
Nausea	11 (19.0)
Constipation	10 (17.2)
Pyrexia	7 (12.1)
Vomiting	5 (8.6)
Oxygen saturation decreased	5 (8.6)
Dizziness	5 (8.6)
Urinary retention	5 (8.6)
Anaemia	4 (6.9)
Headache	4 (6.9)
Pruritus	4 (6.9)
Tachycardia	3 (5.2)
Muscle spasms	3 (5.2)

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of opioids. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system disorder: amnesia, convulsion, memory impairment

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

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

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in OPANA

Immune System Disorders: Angioedema, and other hypersensitivity reactions

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [*see Clinical Pharmacology (12.2)*].

7 DRUG INTERACTIONS

Table ~~2~~4 includes clinically significant drug interactions with OPANA.

Table ~~2~~4: Clinically Significant Drug Interactions with ~~Opana~~OPANA

Alcohol	
Clinical Impact:	The concomitant use of alcohol with OPANA can result in an increase of oxymorphone plasma levels and potentially fatal overdose of oxymorphone.
Intervention:	Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on OPANA therapy [*see Clinical Pharmacology (12.3)*].
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines and other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [*see Warnings and Precautions (5.5)*].
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue OPANA if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [*see Warnings and Precautions (5.3)*]. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.
Intervention:	The use of OPANA is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of OPANA and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Oxymorphone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of OPANA and/or the muscle relaxant as necessary.

Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when OPANA is used concomitantly with anticholinergic drugs.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when OPANA is used concomitantly with anticholinergic drugs.
Cimetidine	
Clinical Impact:	Cimetidine can potentiate opioid-induced respiratory depression.
Intervention:	Monitor patients for respiratory depression when OPANA and cimetidine are used concurrently.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with OPANA in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, reduced postnatal survival of pups and an increased incidence of stillborn pups were observed following oral treatment of pregnant rats with oxymorphone during gestation and through lactation at doses 2.4 and 12 times the human daily dose of 20 mg/day (HDD), respectively. Reduced fetal weights were observed with oral administration of oxymorphone to pregnant rats and rabbits during organogenesis at exposures up to 4.9 and 48.8 times the HDD, respectively [*see Data*]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [*see Warnings and Precautions (5.4)*].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. OPANA is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics,

including OPANA, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

Pregnant rats were treated with oxymorphone hydrochloride from Gestation Day 6 to 17 via oral gavage doses of 5, 10, or 25 mg/kg/day (2.4, 4.9, or 12.2 times the HDD based on body surface area, respectively). Reduced mean fetal weights were observed at 4.9 times the HDD. Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights in all groups and mortality in the high dose group).

Pregnant rabbits were treated with oxymorphone hydrochloride from Gestation Day 7 to 20 via oral gavage doses of 10, 25, or 50 mg/kg/day (9.8, 24.4, or 48.8 times the HDD based on body surface area, respectively). Decreased mean fetal weights were noted at 48.8 times the HDD. Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights).

Pregnant rats were treated with oxymorphone hydrochloride from Gestation Day 6 to Lactation Day 20 via oral gavage doses of 1, 5, 10, or 25 mg/kg/day (0.5, 2.4, 4.9, or 12.2 times the HDD based on body surface area, respectively). Increased neonatal death (postnatal day 0-1) was noted at 2.4 times the HDD. Decreased pup survival over the first week of life, reduced pup birth weight, and reduced postnatal weight gain were noted at 4.9 times the HDD. Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights in all groups and mortality in the 10 and 25 mg/kg/day groups).

In a published study, neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of 153 mg/kg oxymorphone hydrochloride (62.2 times the HDD) on Gestation Day 8 to pregnant hamsters. This dose also produced significant maternal toxicity (20% maternal deaths).

8.2 Lactation

Risk Summary

There is no information regarding the presence of oxymorphone in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OPANA and any potential adverse effects on the breastfed child from OPANA or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to OPANA through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OPANA and any potential adverse effects on the breastfed infant from OPANA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [*see Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

~~Safety~~The safety of oxymorphone was evaluated in two open-label trials in 112 pediatric patients with postoperative pain. In Pediatric Study One, doses of 5, 10, and 15 mg OPANA tablets were evaluated in 58 pediatric patients >12-17 years of age. In Pediatric Study Two, doses of 0.05, 0.10, and 0.20 mg/kg of oxymorphone HCL 1mg/mL oral solution were evaluated in 54 pediatric patients 2-≤12 years of age.

The most frequent adverse events observed in the 2-≤12 years old age group were pyrexia, nausea, and vomiting. The most frequent adverse events observed in the >12-17 years old age group were nausea, constipation, and pyrexia [*see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Trials (14)*].

The safety and effectiveness of OPANA in ~~pediatric patients below the age of 18~~children <2 years of age have not been established.

8.5 Geriatric Use

OPANA should be used with caution in elderly patients [*see Clinical Pharmacology (12.3)*].

Of the total number of subjects in clinical studies of OPANA, 31% were 65 and over, while 7% were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects. 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. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of OPANA slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [*see Warnings and Precautions (5.6)*].

Oxymorphone is known to be substantially excreted by the kidney and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because the elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

In a study of extended-release oxymorphone tablets, patients with mild hepatic impairment were shown to have an increase in bioavailability compared to the subjects with normal hepatic function. OPANA should be used with caution in patients with mild impairment. These patients should be started with the lowest dose (5 mg) and titrated slowly while carefully monitoring for signs of respiratory and central nervous system depression. OPANA is contraindicated for patients with moderate and severe hepatic impairment [*see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.15), and Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

In a study of extended-release oxymorphone tablets, patients with moderate to severe renal impairment were shown to have an increase in bioavailability compared to the subjects with normal renal function [*see Clinical Pharmacology (12.3)*]. Such patients should be started be started with the lowest dose (5 mg) and titrated slowly while monitoring for signs of respiratory and central nervous system depression [*see Dosage and Administration (2.4) Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OPANA contains oxymorphone, a Schedule II controlled substance.

9.2 Abuse

OPANA contains oxymorphone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone and tapentadol. OPANA can be abused and is subject to misuse, addiction, and criminal diversion [*see Warnings and Precautions (5.1)*].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(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.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

OPANA, 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 and federal 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 limit abuse of opioid drugs.

Risks Specific to Abuse of OPANA

OPANA is for oral use only. Abuse of OPANA poses a risk of overdose and death. This risk is increased with concurrent abuse of OPANA with alcohol and other central nervous system depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

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 should not be abruptly discontinued in a physically-dependent patient [*see Dosage and Administration (2.8)*]. If OPANA is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [*see Warnings and Precautions (5.4), Use in Specific Populations (8.1)*].

10 OVERDOSAGE

Clinical Presentation

Acute overdose with OPANA can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [*see Clinical Pharmacology (12.2)*].

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to oxymorphone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxymorphone overdose.

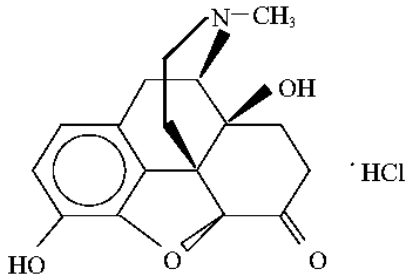
Because the duration of opioid reversal is expected to be less than the duration of action of oxymorphone in OPANA, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

OPANA (oxymorphone hydrochloride) tablet is an opioid agonist available in 5 mg and 10 mg tablet strengths for oral administration. The chemical name for oxymorphone hydrochloride is 4, 5α-epoxy-3,

14-dihydroxy-17-methylmorphinan-6-one hydrochloride. The molecular weight is 337.80. The molecular formula is $C_{17}H_{19}NO_4 \cdot HCl$ and it has the following chemical structure.



Oxymorphone hydrochloride is white to off white odorless powder, which is sparingly soluble in alcohol and ether, but freely soluble in water.

The inactive ingredients in OPANA include: lactose monohydrate, magnesium stearate, and pregelatinized starch. In addition, the 5 mg tablets contain FD&C blue No. 2 aluminum lake. The 10 mg tablets contain D&C red No. 30 aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxymorphone is a full opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxymorphone is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with oxymorphone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Oxymorphone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Oxymorphone causes 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 origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Oxymorphone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Oxymorphone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [*see Adverse Reactions (6.2)*]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [*see Adverse Reactions (6.2)*].

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

The minimum effective analgesic concentration varies widely among patients, especially among patients who have been previously treated with potent agonist opioids The minimum effective analgesic concentration of oxymorphone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance [*see Dosage and Administration (2.1, 2.2)*].

Concentration–Adverse Reaction Relationships

There is a relationship between increasing oxymorphone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [*see Dosage and Administration (2.1, 2.2, 2.6)*].

12.3 Pharmacokinetics

Absorption

The absolute oral bioavailability of oxymorphone is approximately 10%. Studies in healthy volunteers reveal predictable relationships between OPANA dosage and plasma oxymorphone concentrations.

Steady-state levels were achieved after three days of multiple dose administration. Under both single-dose and steady-state conditions, dose proportionality has been established for 5 mg, 10 mg and 20 mg doses of OPANA, for both peak plasma levels (C_{max}) and extent of absorption (AUC) (see Table ~~3~~5).

Table ~~3~~5: Mean (±SD) OPANA Pharmacokinetic Parameters				
Regimen	**Dosage**	**C_{max} (ng/mL)**	**AUC (ng·hr/mL)**	**$T_{1/2}$ (hr)**
Single Dose	5 mg 10 mg 20 mg	1.10±0.55 1.93±0.75 4.39±1.72	4.48±2.07 9.10±3.40 20.07±5.80	7.25±4.40 7.78±3.58 9.43±3.36
Multiple Dose [a]	5 mg 10 mg 20 mg	1.73±0.62 3.51±0.91 7.33±2.93	4.63±1.49 10.19±3.34 21.10±7.59	NA NA NA
NA = not applicable [a] Results after 5 days of every 6 hours dosing.				

After oral dosing with 40 mg of OPANA in healthy volunteers under fasting conditions or with a high-fat meal, the C_{max} and AUC were increased by approximately 38% in fed subjects relative to fasted subjects. As a result, OPANA should be dosed at least one hour prior to or two hours after eating [*see Dosage and Administration (2.1)*].

The oxymorphone HCl 1 mg/mL oral solution used in Pediatric Study Two was shown to be bioequivalent to OPANA in healthy adults under fasting conditions.

Distribution

Formal studies on the distribution of oxymorphone in various tissues have not been conducted. Oxymorphone is not extensively bound to human plasma proteins; binding is in the range of 10% to 12%.

Elimination

~~Opana half~~Half-life ranges from approximately 9-11 hours after a single oral dose (5-40 mg).

Metabolism

Oxymorphone is highly metabolized, principally in the liver, and undergoes reduction or conjugation with glucuronic acid to form both active and inactive products. The two major metabolites of oxymorphone are oxymorphone-3-glucuronide and 6-OH-oxymorphone. The mean plasma AUC for oxymorphone-3-glucuronide is approximately 90-fold higher than the parent compound. The pharmacologic activity of the glucuronide metabolite has not been evaluated. 6-OH-oxymorphone has been shown in animal studies to have analgesic bioactivity. The mean plasma 6-OH-oxymorphone AUC is approximately 70% of the oxymorphone AUC following single oral doses but is essentially equivalent to the parent compound at steady-state.

Excretion

Because oxymorphone is extensively metabolized, <1% of the administered dose is excreted unchanged in the urine. On average, 33% to 38% of the administered dose is excreted in the urine as oxymorphone-3-glucuronide and 0.25% to 0.62% is excreted as 6-OH-oxymorphone in subjects with normal hepatic and renal function. In animals given radiolabeled oxymorphone, approximately 90% of the administered radioactivity was recovered within 5 days of dosing. The majority of oxymorphone-derived radioactivity was found in the urine and feces.

Specific Populations

Age: Pediatric Population

Based on two open-label trials in 112 pediatric patients with postoperative pain, on a weight adjusted basis, the exposure levels as well as the half-life of oxymorphone appeared similar among patients 2 to ≤12 and >12 to 17 years of age and the adult population [*see Use in Specific Populations (8.4)*].

Age: Geriatric Population

The plasma levels of oxymorphone administered as an extended-release tablet were about 40% higher in elderly (≥65 years of age) than in younger subjects [*see Use in Specific Populations (8.5)*].

Sex:

The effect of sex on the pharmacokinetics of OPANA has not been studied. In a study with an extended-release formulation of oxymorphone, there was a consistent tendency for female subjects to have slightly higher AUC_{ss} and C_{max} values than male subjects. However, sex differences were not observed when AUC_{ss} and C_{max} were adjusted by body weight.

Hepatic Impairment

The liver plays an important role in the pre-systemic clearance of orally administered oxymorphone. Accordingly, the bioavailability of orally administered oxymorphone may be markedly increased in patients with moderate to severe liver disease. The effect of hepatic impairment on the pharmacokinetics of OPANA has not been studied. However, in a study with an extended-release formulation of oxymorphone, the disposition of oxymorphone was compared in 6 patients with mild, 5 patients with moderate, and one patient with severe hepatic impairment, and 12 subjects with normal hepatic function. The bioavailability of oxymorphone was increased by 1.6-fold in patients with mild hepatic impairment and by 3.7-fold in patients with moderate hepatic impairment. In one patient with severe hepatic impairment, the bioavailability was increased by 12.2-fold. The half-life of oxymorphone was not significantly affected by hepatic impairment.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of OPANA has not been studied. However, in a study with an extended-release formulation of oxymorphone, an increase of 26%, 57%, and 65% in oxymorphone bioavailability was observed in mild (creatinine clearance 51-80 mL/min; n=8), moderate (creatinine clearance 30-50 mL/min; n=8), and severe (creatinine clearance <30 mL/min; n=8) patients, respectively, compared to healthy controls.

Drug Interactions Studies

In vitro studies revealed little to no biotransformation of oxymorphone to 6-OH-oxymorphone by any of the major cytochrome P450 (CYP P450) isoforms at therapeutically relevant oxymorphone plasma concentrations.

No inhibition of any of the major CYP P450 isoforms was observed when oxymorphone was incubated with human liver microsomes at concentrations of ≤50 μM. An inhibition of CYP 3A4 activity occurred at oxymorphone concentrations ≥150 μM. Therefore, it is not expected that oxymorphone, or its metabolites will act as inhibitors of any of the major CYP P450 enzymes *in vivo*.

Increases in the activity of the CYP 2C9 and CYP 3A4 isoforms occurred when oxymorphone was incubated with human hepatocytes. However, clinical drug interaction studies with OPANA ER showed no induction of CYP450 3A4 or 2C9 enzyme activity, indicating that no dose adjustment for CYP 3A4- or 2C9-mediated drug-drug interactions is required.

Alcohol Interaction

The effect of co-ingestion of alcohol with OPANA has not been evaluated. However, an in vivo study was performed to evaluate the effect of alcohol (40%, 20%, 4% and 0%) on the bioavailability of a single dose of 40 mg of extended-release oxymorphone tablets in healthy, fasted volunteers. Following concomitant administration of 240 mL of 40% ethanol the C_{max} increased on average by 70% and up to 270% in individual subjects. Following the concomitant administration of 240 mL of 20% ethanol, the C_{max} increased on average by 31% and up to 260% in individual subjects. In some individuals there was also a decrease in oxymorphone peak plasma concentrations. No effect on the release of oxymorphone

from the extended-release tablet was noted in an in vitro alcohol interaction study. The mechanism of the in vivo interaction is unknown. Therefore, avoid co-administration of oxymorphone and ethanol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenic potential was observed in long-term animal studies in mice and rats. Oxymorphone hydrochloride was administered to Sprague Dawley rats (2.5, 5, and 10 mg/kg/day in males and 5, 10, and 25 mg/kg/day in females) for 2 years by oral gavage. Systemic drug exposure (AUC) at the highest doses tested in male and female rats was 4.8 times and 21.2 times the human exposure at a dose of 20 mg/day, respectively. Oxymorphone hydrochloride was administered to male and female CD-1 mice (10, 25, 75 and 150 mg/kg/day) for 2 years by oral gavage. Systemic drug exposure (AUC) at 150 mg/kg/day in male and female mice was 205 times and 243 times the human exposure at a dose of 20 mg/day, respectively.

Mutagenesis

Oxymorphone hydrochloride was not mutagenic when tested in the *in vitro* bacterial reverse mutation assay (Ames test), or in an in vitro mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes. Oxymorphone hydrochloride tested positive in both the rat and mouse in vivo micronucleus assays. An increase in micronucleated polychromatic erythrocytes occurred in mice given doses of ≥250 mg/kg and in rats given doses of 20 and 40 mg/kg. A subsequent study demonstrated that oxymorphone hydrochloride was not aneugenic in mice following administration of up to 500 mg/kg. Additional studies indicate that the increased incidence of micronucleated polychromatic erythrocytes in rats may be secondary to increased body temperature following oxymorphone administration. Doses associated with increased micronucleated polychromatic erythrocytes also produce a marked, rapid increase in body temperature. Pretreatment of animals with sodium salicylate minimized the increase in body temperature and prevented the increase in micronucleated polychromatic erythrocytes after administration of 40 mg/kg oxymorphone.

Impairment of ~~fertility~~Fertility

Female rats were treated with oxymorphone hydrochloride beginning 14 days prior to mating through Gestation Day 7 via oral gavage doses of 5, 10, or 25 mg/kg/day (2.4, 4.9, or 12.2 times the human daily dose of 20 mg/day based on body surface area, respectively). Male rats were treated via oral gavage with the same oxymorphone hydrochloride doses beginning 28 days prior to and throughout mating. In female rats, an increase in the length of the estrus cycle and decrease in the mean number of viable embryos, implantation sites and corpora lutea were observed at 4.9 times the human dose of 20 mg/day. No adverse effects of oxymorphone on male reproductive function or sperm parameters were observed.

14 CLINICAL STUDIES

The analgesic efficacy of OPANA has been evaluated in acute pain following orthopedic and abdominal surgeries.

14.1 Orthopedic Surgery

Two double-blind, placebo-controlled, dose-ranging studies in patients with acute moderate to severe pain following orthopedic surgery evaluated the doses of OPANA 10 mg and 20 mg, and 30 mg was included in one study. Both studies demonstrated that OPANA 20 mg provided greater analgesia as measured by total pain relief based on a weighted analysis over 8 hours using a 0-4 categorical, compared to placebo. OPANA 10 mg provided greater analgesia as compared to placebo in one of the two studies. There was

no evidence of superiority of the 30 mg dose over the 20 mg dose. However, there was a high rate of naloxone use in patients receiving the OPANA 30 mg dose in the ~~post-operative~~postoperative period [*see Dosage and Administration (2.2)*].

14.2 Abdominal Surgery

In a randomized, double-blind, placebo-controlled, multiple-dose study, the efficacy of OPANA 10 mg and 20 mg was assessed in patients with moderate to severe acute pain following abdominal surgery. In this study, patients were dosed every 4 to 6 hours over a 48-hour treatment period. OPANA 10 and 20 mg provided greater analgesia, as measured by the mean average pain intensity on a 0-100 mm visual analog scale, over 48 hours, compared to placebo [*see Dosage and Administration (2.2)*].

14.3 Pediatric Postoperative Pain

Oxymorphone has been evaluated in two open-label clinical trials of 112 pediatric patients with postoperative pain. In Pediatric Study One, doses of 5, 10, and 15 mg OPANA tablets were evaluated in 58 patients >12-17 years of age. In Pediatric Study Two, doses of 0.05, 0.10, and 0.20 mg/kg of oxymorphone HCl 1 mg/mL oral solution were evaluated in 54 patients 2-≤12 years of age. Both the oral solution and tablet were generally safe and well tolerated for postoperative pain. Overall, the safety profile was consistent with the known safety profile of OPANA IR tablets in adults.

16 HOW SUPPLIED/STORAGE AND HANDLING

OPANA (oxymorphone hydrochloride) tablets are supplied as follows:

5 mg Tablet:

Blue, round, convex tablets debossed with E612 over 5 on one side and plain on the other.

Bottles of 100 tablets with child-resistant closure	NDC 63481-612-70
Unit-Dose package of 100 tablets (5 blister cards of 20 tablets, not child-resistant, for hospital use only)	NDC 63481-612-75

10 mg Tablet:

Red, round, convex tablets debossed with E613 over 10 on one side and plain on the other.

Bottles of 100 tablets with child-resistant closure	NDC 63481-613-70
Unit-Dose package of 100 tablets (5 blister cards of 20 tablets, not child-resistant, for hospital use only)	NDC 63481-613-75

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

Dispense in tight container as defined in the USP, with a child-resistant closure (as required).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Addiction, Abuse, and Misuse

Inform patients that the use of OPANA, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [*see Warnings and Precautions (5.1)*]. Instruct patients not to share OPANA with others and to take steps to protect OPANA from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting OPANA or when the dosage is increased, and that it can occur even at recommended dosages [*see Warnings and Precautions (5.3)*]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [*see Warnings and Precautions (5.3)*]. Instruct patients to take steps to store OPANA securely and to dispose of unused OPANA by flushing the tablets down the toilet.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if OPANA is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider [*see Warnings and Precautions (5.5), Drug Interactions (7)*].

Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions

Inform patients that anaphylaxis, angioedema, and other hypersensitivity reactions have been reported with ingredients contained in OPANA. Advise patients how to recognize such a reaction and when to seek medical attention [*see Contraindications (4), Warnings and Precautions (5.7), Adverse Reactions (6)*].

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications~~.~~ [*see Drug Interactions (7~~)~~*])].

MAOI Interaction

Inform patients to avoid taking OPANA while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking OPANA [*see Drug Interactions (7)*].

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [*see Warnings and Precautions (5.8)*].

Important Administration Instructions

Instruct patients how to properly take OPANA exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression).

- Advise patients not to adjust the dose of OPANA without consulting with a physician or other healthcare professional.
- If patients have been receiving treatment with OPANA for more than a few weeks and cessation of therapy is indicated, counsel them on the importance of safely tapering the dose as abrupt discontinuation of the medication could precipitate withdrawal symptoms. Provide a dose schedule to accomplish a gradual discontinuation of the medication [*see Dosage and Administration (2.8)*].

Hypotension

Inform patients that OPANA may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) [*see Warnings and Precautions (5.9)*].

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of OPANA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [*see Warnings and Precautions (5.4), Use in Specific Populations (8.1)*].

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that OPANA can cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy [*see Use in Specific Populations (8.1), Warnings and Precautions (5.4)*].

Lactation

Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs [*see Use in Specific Populations (8.1)*].

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [*see Adverse Reactions (6.2)*].

Driving or Operating Heavy Machinery

Inform patients that OPANA may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [*see Warnings and Precautions (5.14)*].

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [*see Adverse Reactions (6)*].

Disposal of Unused OPANA

Dispose of any unused tablets from a prescription by flushing them down the toilet as soon as they are no longer needed.

Distributed by:
Endo Pharmaceuticals Inc.
Malvern, PA 19355

Manufactured by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

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Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology (OSE)

Office of Pharmacovigilance and Epidemiology (OPE)

Drug Utilization Review

Date:	August 21, 2019
Reviewer:	Ibrahim T. Ibrahim, Pharm.D., MPH Drug Utilization Data Analyst Division of Epidemiology II
Team Leader:	Rajdeep Gill, Pharm.D. Drug Utilization Data Analysis Team Leader Division of Epidemiology II
Deputy Director: for Drug Utilization:	LCDR Grace Chai, PharmD Division of Epidemiology II Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology
Subject:	U.S. Outpatient Utilization Patterns of Opioid Analgesics: Pediatric Advisory Committee Meeting
Drug Name(s):	Opioid Analgesics
Application Type/Number:	Multiple
Applicant/Sponsor:	Multiple
OSE RCM #:	2018-2034

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

CONTENTS

EXECUTIVE SUMMARY

The Office of Surveillance and Epidemiology (OSE) conducted this drug utilization review in support of assessments conducted under the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on drug utilization patterns of opioid analgesics in pediatric patients 0-17 years old in U.S. outpatient retail pharmacies. The review will be used as background information to provide context for the upcoming Pediatric Advisory Committee (PAC) meeting in September 2019.

An estimated 1.8 million pediatric patients (ages 0-17 years) received prescriptions dispensed for opioid analgesics from U.S. outpatient retail pharmacies in 2018, accounting for 3.5% of the estimated number of total patients dispensed opioid analgesics. Combination hydrocodone-acetaminophen, codeine-acetaminophen, oxycodone-acetaminophen products, followed by single-ingredient oxycodone immediate-release (IR) and single-ingredient tramadol were the most frequently dispensed opioid analgesic prescriptions among pediatric patients 0-17 years old in 2018. During the examined time-period, there was a 59% decrease in pediatric utilization of opioid analgesics by 2018 compared to 2009, driven by decreases in hydrocodone-acetaminophen, codeine-acetaminophen, and oxycodone-acetaminophen products. The estimated number of pediatric patients who received prescriptions dispensed for single-ingredient oxycodone IR appears to have increased from 31,000 patients in 2009 to 150,000 patients in 2018. Based on opioid analgesic dispensed prescription claims data, urology and surgical specialists were the top prescribers for pediatric patients < 2 years old. Otolaryngology, surgical specialties and dentists were the top prescribers for patients 2-11 years old. Surgical specialties, dentists and nurse practitioner/physician assistants (NP/PA) were the top prescribers for patients 12-17 years old in 2018. Based on U.S. office-based physician survey data, opioid analgesics were mainly mentioned in association with diagnoses for the management of acute conditions such as fractures, injuries, and inguinal hernia etc., among pediatric patients in 2018.

1. INTRODUCTION

The Office of Surveillance and Epidemiology (OSE) conducted this drug utilization review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on drug utilization patterns of opioid analgesics in pediatric patients 0-17 years old in U.S. outpatient retail pharmacies. The drug utilization analyses in this review will be used as background information to provide context for the upcoming Pediatric Advisory Committee (PAC) meeting in September 2019.

2. METHODS AND MATERIALS

This drug utilization review was conducted using proprietary databases available to the FDA (See Appendix B for full database descriptions).

2.1 PRODUCTS INCLUDED

Table 1 below shows the opioid analgesics included in this review (including all extended-release/long-acting, immediate-release, transdermal and suppository formulations). This review focused on non-injectable opioid analgesics mainly dispensed in the outpatient retail pharmacy setting. We did not include injectable formulations of opioid analgesics, opioid-containing Medication-Assisted Therapy (MAT) products and opioid-containing cough/cold products in this review.

TABLE.1

Extended-Release/Long-Acting Formulation (ER/LA)	**Immediate-Release Formulation (IR)**
• Buprenorphine Transdermal • Buprenorphine • Fentanyl Transdermal • Hydrocodone • Hydromorphone • Methadone • Morphine • Morphine-Naltrexone • Oxycodone • Oxycodone-Acetaminophen • Oxymorphone • Tapentadol • Tramadol	• Butalbital • Butorphanol • Codeine • Codeine-Acetaminophen • Dihydrocodeine-aspirin-caffeine • Dihydrocodeine-acetaminophen-caffeine • Hydrocodone-Acetaminophen • Hydrocodone-Aspirin • Hydrocodone-Ibuprofen • Hydromorphone • Levorphanol • Meperidine • Meperidine-Promethazine • Morphine • Opium • Oxycodone • Oxycodone-Acetaminophen • Oxycodone-Aspirin • Oxycodone-Ibuprofen • Oxymorphone • Pentazocine-Acetaminophen • Pentazocine-Naloxone • Propoxyphene • Propoxyphene-Acetaminophen • Tapentadol • Tramadol • Tramadol-Acetaminophen • Transmucosal Immediate-Release Fentanyl (TIRF)

2.2 DETERMINING SETTINGS OF CARE

The primary setting of care for utilization of opioid analgesics was determined based on sales volume (bottles or packages) from manufacturers in 2018 using the IQVIA National Sales Perspectives™ (NSP) database.

2.3 OUTPATIENT RETAIL UTILIZATION DATA

The annual estimates of patients, stratified by patient age (<2, 2-11, 12-17 years old), who received prescriptions dispensed for opioid analgesics from U.S. outpatient retail pharmacies from 2009 through 2018 were determined using the IQVIA Total Patient Tracker™ (TPT) database.

The estimated number of prescriptions dispensed for opioid analgesics to pediatric patients (<2, 2-11, 12-17 years old) in 2018, stratified by prescriber specialties from U.S. outpatient retail pharmacies was determined using the IQVIA National Prescription Audit™ (NPA) database .

2.4 OFFICE-BASED PHYSICIAN SURVEY DATA

Diagnoses associated with the use of opioid analgesics in pediatric patients (<2, 2-11, 12-17 years old) as reported by U.S. office-based physician surveys in 2018 were examined using the Syneos Health Research & Insights LLC., TreatmentAnswers™ with Pain Panel database. Diagnoses data are reported as drug use mentions based on International Classification of Diseases, Tenth Revisions, Clinical Modification (ICD-10-CM) codes with 95% confidence intervals. Estimates of drug use mentions are obtained from surveys of a sample of 3,200 office-based physicians with 115 pain specialists reporting on patient activity during one day per month. These survey data provide insight into prescriber intent; but are not directly linked to dispensed prescriptions. A drug use mention indicates that a specific drug was mentioned in association with a diagnosis during an office visit, but it does not necessarily result in a prescription being generated.

3. RESULTS

3.1 SETTINGS OF CARE

Based on manufacturer sales distribution data in 2018, approximately 71% of all bottles or packages of opioid analgesics were sold to outpatient retail pharmacies, followed by 28% to non-retail pharmacies, and 1% to mail-order/specialty pharmacies.[1] Therefore, the utilization patterns from outpatient retail pharmacies where non-injection opioid analgesics are primarily utilized are examined in this review.

3.2 U.S. OUTPATIENT RETAIL PHARMACY DATA

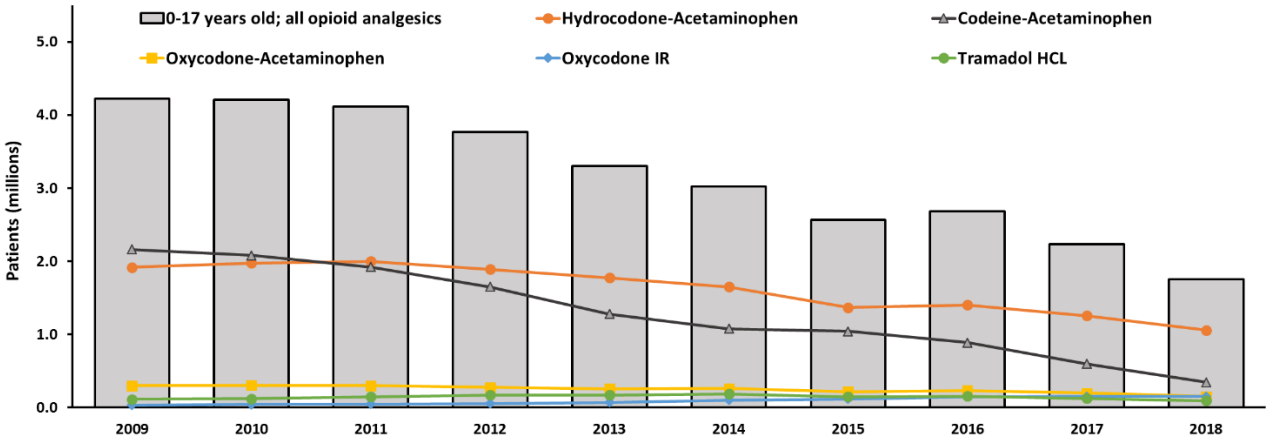
Table 2 in **Appendix A** provides estimates of the number of pediatric patients (0-17 years old) who received prescriptions dispensed for opioid analgesics from U.S. outpatient retail pharmacies, stratified by patient age from 2009 through 2018, annually. Pediatric patients (0-17 years) accounted for 3.5% (1.8 million patients) of the estimated total of 50 million patients of all

[1] IQVIA™ National Sales Perspectives. Year 2018. Extracted July 2019. File NSP OA Market.xlsx

ages who received opioid analgesic dispensed prescriptions in 2018. Utilization of opioid analgesics by pediatric patients appears to have decreased from an estimated 4.2 million patients in 2009 to 1.8 million patients in 2018, a 59% decrease. Additionally, the proportion of all patients who received dispensed prescriptions for opioid analgesics who were pediatric decreased from 6.5% in 2009 to 3.5% of total patients in 2018.

As illustrated in **Figure 1 below and Table 3 in Appendix A**, the frequently dispensed opioid analgesics prescriptions among pediatric patients (0-17 years old) were hydrocodone-acetaminophen, codeine-acetaminophen, oxycodone-acetaminophen, single-ingredient oxycodone IR and tramadol products. Approximately 51% of the estimated number of pediatric patients received a dispensed prescription for codeine-acetaminophen in 2009, but from 2011-2018 more pediatric patients received hydrocodone-acetaminophen dispensed prescription than any other opioid analgesics. During the examined time-period, utilization of opioid analgesics decreased in pediatric patients (ages 0-17 years), while the number of patients who received prescriptions dispensed for single-ingredient oxycodone appears to have increased from an estimated 31,000 pediatric patients in 2009 to 150,000 pediatric patients in 2018.

Figure 1. Estimated number of pediatric patients* (0-17 years old) who received prescriptions dispensed for <u>all</u> opioid analgesics (grey bar) and for the top 5 opioid analgesics (solid lines), from U.S. outpatient retail pharmacies, 2009-2018

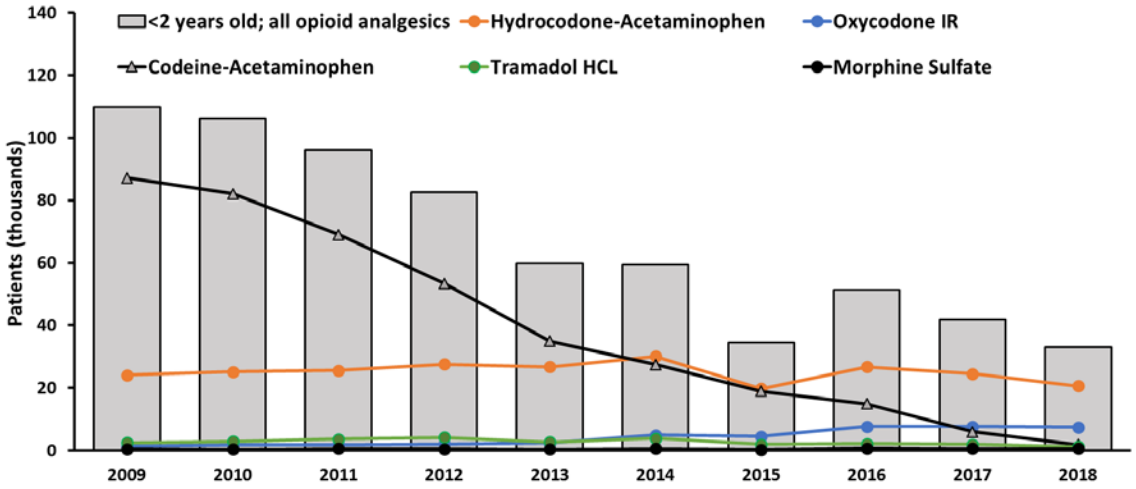


Data Source: IQVIA Total Patient Tracker™. 2009-2018. File: TPT USC 022 by Age_2009-2018_7_18_19xlsx. Data extracted July 2019.
Of note, there are changes in the underlying data and methodology of the proprietary database IQVIA NPA to account for a dynamic pharmaceutical market, including a change to manage prescription claims that are voided or reversed, prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017, data prior to January 2017 have not been adjusted to the new methodology. In 2018, an estimated 2% of total prescription claims for opioid analgesics dispensed from U.S. retail pharmacies appears to have been voided or reversed.
*Note: Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients age 0-17 years include patients less than 18 years of age (17 years and 11 months).

Figure 2 shows the top five utilized opioid analgesic prescriptions dispensed to patients < 2 years old (hydrocodone-acetaminophen, single-ingredient oxycodone IR, codeine-acetaminophen, single-ingredient tramadol and single-ingredient morphine sulfate). Pediatric patients < 2 years old accounted for an estimated 2% of the total pediatric patients ages 0-17 years old in 2018. The estimated number of patients <2 years old appears to have decreased by 70% from 2009 to 2018. The most frequently utilized opioid analgesic in 2009 was codeine-

acetaminophen (79%). From 2014 onwards, hydrocodone-acetaminophen was the top utilized opioid analgesic accounting for 62% of pediatric patients in 2018. The estimated number of patients < 2 years old who were prescribed codeine-acetaminophen decreased by 98% from 2009 to 2018. The estimated number of patients < 2 years old who received single-ingredient oxycodone IR appears to have increased from an estimated 1,000 patients in 2009 to 7,000 patients in 2018.

Figure 2. Estimated number of pediatric patients* (< 2 years old) who received prescriptions dispensed for <u>all</u> opioid analgesics (grey bar) and for the top 5 opioid analgesics (solid lines), from U.S. outpatient retail pharmacies, 2009-2018



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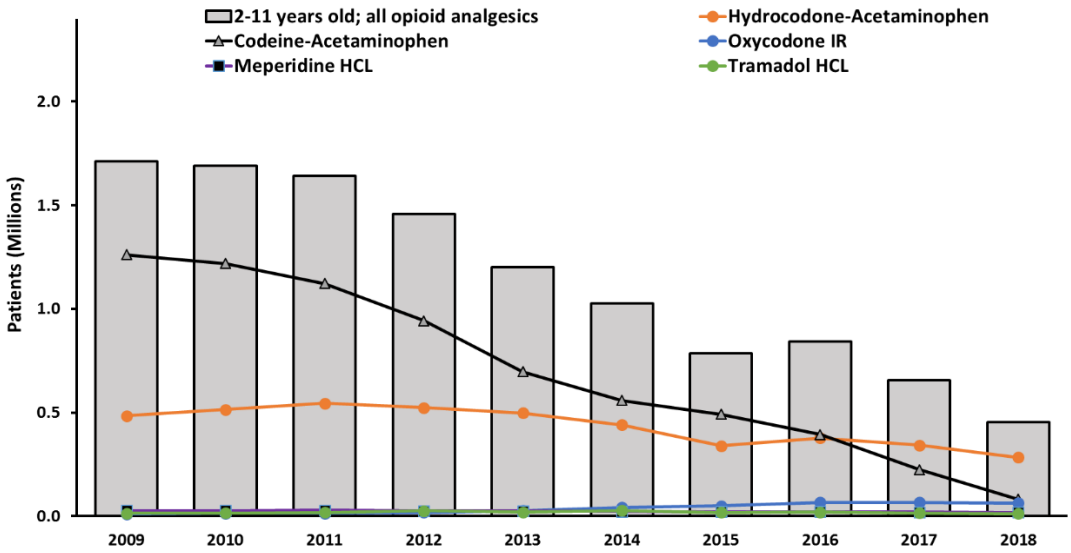
*Note: Patient age groups are inclusive of all patients up to the day before their next birthday.

Figure 3 shows the top 5 opioid analgesic prescriptions dispensed to patients 2-11 years old (hydrocodone-acetaminophen, codeine-acetaminophen, single-ingredient oxycodone, meperidine and single-ingredient tramadol respectively). Pediatric patients 2-11 years old accounted for an estimated 26% of the total pediatric patients ages 0-17 years old in 2018. The estimated number of patients 2-11 years old decreased by 73% from 2009 to 2018. The most utilized opioid analgesic in 2009 was codeine-acetaminophen (74%). Hydrocodone-acetaminophen became the most frequently utilized opioid analgesic (52%) in 2017 and increased to 62% of the total in patients 2-11 years old in 2018. The estimated number of patients ages 2-11 years prescribed codeine-acetaminophen decreased by 94% from 2009 to 2018. The estimated number of patients 2-11 years old who received single-ingredient oxycodone IR appears to have increased from an estimated 9,000 patients in 2009 to 63,000 in 2018.

Figure 3. Estimated number of pediatric patients* (2-11 years old) who received prescriptions dispensed for all opioid analgesics (grey bar) and for the top 5 opioid analgesics (solid lines), from U.S. outpatient retail pharmacies, 2009-2018



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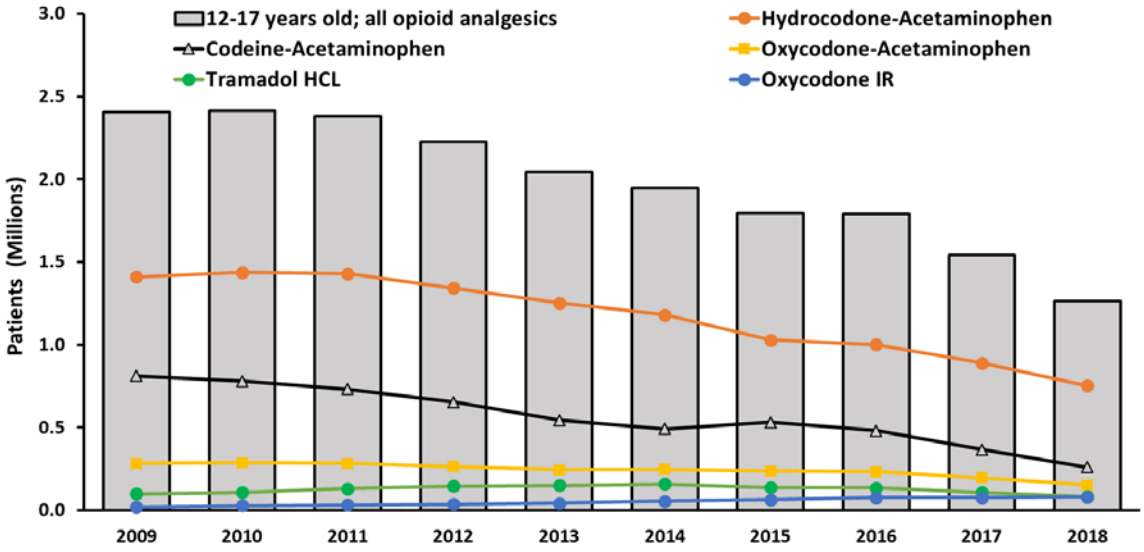
*Note: Patient age groups are inclusive of all patients up to the day before their next birthday.

Figure 4 shows the top 5 opioid analgesic prescriptions dispensed to patients 12-17 years old (hydrocodone-acetaminophen, codeine-acetaminophen, oxycodone-acetaminophen, single ingredient tramadol and single ingredient oxycodone). Pediatric patients 12-17 years old accounted for 72% of the total pediatric patients ages 0-17 years old in 2018. The estimated number of patients 12-17 years decreased by 47% from 2009 to 2018. Hydrocodone-acetaminophen was the most utilized opioid analgesic in this age group throughout the study period, followed by codeine-acetaminophen. The estimated number of patients 12-17 years old who received single-ingredient oxycodone IR appears to have increased from an estimated 19,000 patients in 2009 to 80,000 in 2018.

Figure 4. Estimated number of pediatric patients* (12-17 years old) who received prescriptions dispensed for all opioid analgesics (grey bar) and for the top 5 opioid analgesics (solid lines), from U.S. outpatient retail pharmacies, 2009-2018



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*Note: Patient age groups are inclusive of all patients up to the day before their next birthday.

3.3 PRESCRIBER SPECIALTIES

Table 4 in Appendix A provides the top prescriber specialties for opioid analgesic prescriptions dispensed from U.S. outpatient retail pharmacies in 2018. Of the estimated 168 million prescriptions dispensed to all ages, pediatric patients 0-17 years old accounted for 1.2% of the total or 2.1 million prescriptions dispensed in 2018.

Among pediatric patients, opioid analgesic prescriptions dispensed to patients < 2 years old accounted for approximately 2% of the total or 36,000 prescriptions. Urology specialists accounted for approximately 31%, followed by surgical specialties at 15% and NP/PA at 11% of the total opioid analgesic prescriptions dispensed to patients < 2 years old.
Opioid analgesic prescriptions dispensed to patients 2-11 years old accounted for approximately 25% of the total or 527,000 prescriptions in 2018. Otolaryngology specialists accounted for approximately 26%, followed by surgical specialties at 18% and dentistry at 12% of the total opioid analgesic prescriptions dispensed to patients 2-11 years old in 2018.
Opioid analgesic prescriptions dispensed to pediatric patients 12-17 years of age accounted for approximately 73% of the total or 1.5 million prescriptions in 2018. Surgical specialties accounted for approximately 46%, followed by dentistry at 16% and NP/PA at 10% of the total opioid analgesic prescriptions dispensed to patients 12-17 years old in 2018.

3.4 OFFICE-BASED PHYSICIAN SURVEY DATA

Table 5 in Appendix A provides the top diagnosis (ICD-10-CM) by drug use mentions as reported by U.S office-based physician surveys associated with the use of opioid analgesics for pediatric patients 0-17 years old in 2018. For patients <2 years old, fractures and injuries (ICD-10 codes S00-T14) and other and unspecified soft tissue disorders, not elsewhere classified (ICD-10 code M79) were the only reported ICD-10 codes. Pediatric patients 2-11 years old had fractures and injuries (ICD-10 codes S00-T14) and Inguinal hernia (ICD-10 code K-40) as the top reported diagnoses. Fractures and injuries (ICD-10 codes S00-T14), scoliosis (ICD-10 M41) and other joint disorders, not elsewhere classified (ICD-10 code M25) respectively were the top three reported diagnoses for pediatric patients 12-17 years old in 2018.

4. DISCUSSION

This review focuses on drug utilization patterns of opioid analgesics in pediatric patients 0-17 years old in U.S. outpatient retail pharmacies to provide context for discussion during the upcoming Pediatric Advisory Committee (PAC) meeting in September 2019. Our findings showed that in 2018, an estimated 1.8 million pediatric patients 0-17 years old (approximately 3.5% of the estimated total 50 million patients of all ages) received dispensed prescriptions for opioid analgesic products from U.S. outpatient retail pharmacies. The highest proportion of pediatric opioid analgesic use was in patients 12-17 years old. The number of pediatric patients 0-17 years who received prescriptions dispensed for opioid analgesics appears to have decreased by 59% from 2009 compared to 2018. Although the reasons for this decrease cannot be identified with our analyses alone, a similar decline in opioid analgesic use was also observed among adult patients during the study period. Among all the pediatric age groups, the most utilized opioids analgesics were combination hydrocodone-acetaminophen and codeine-acetaminophen in 2018.

Codeine-acetaminophen was the top most utilized opioid analgesic by pediatric patients 0-17 years old in 2009 and 2010, after which hydrocodone-acetaminophen became the top utilized opioid analgesic. The overall pediatric utilization of codeine-acetaminophen decreased by an estimated 84% from 2009 through 2018. The largest decrease appeared to be in patients 0-1 year (97%) and 2-11 years (94%). This decrease may have been driven in part by numerous regulatory actions taken by the agency. For example, in 2013, FDA issued a Boxed Warning and Contraindication for patients 18 years and younger regarding the risk of life-threatening respiratory depression following codeine use for pain management along with multiple other regulatory actions throughout the years.[2] The FDA added a contraindication warning in 2017 for codeine and tramadol use in patients 0-11 years and a warning on the label for patients 12-18 years of age.[3] Utilization of single-ingredient oxycodone IR in pediatric population appears to have increased from an estimated 31,000 pediatric patients in 2009 to 150,000 pediatric patients in 2018. Analysis of dispensed prescriptions in pediatric patients reveals that

[2] U. S. Food and Drug Administration (2013). Drug Safety Communications. Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy. Accessed 27 July 2019. http://wayback.archive-it.org/7993/20170722185707/https://www.fda.gov/Drugs/DrugSafety/ucm339112.htm

[3] U. S. Food and Drug Administration (2017). Drug Safety Communications. FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. Accessed 27 July 2019. https://www.fda.gov/media/104268/download

prescriptions for opioid analgesics were most frequently written by surgical specialist (such as, general surgery, neurological surgery, orthopedic surgery, etc.) in 2018.

The patient estimates are nationally projected based on a sample of prescriptions claims from retail pharmacies and should be interpreted with caution as some estimates may be based on a small sample sizes, particularly for the pediatric population. Data are based on prescription transaction and claims records and some data may be a result of errors such as wrong date of birth on prescriptions; however, medical charts were not available for validation. Summarization of the projected estimates across patient age groups, time periods, and/or products may lead to differences in patient count due to rounding attributable to the projection methodology utilized. Moreover, patient estimates may be double counted across patient age groups, time periods, and/or products due to patients aging or receiving multiple products during the study period. This analysis focused on data from the outpatient retail pharmacy setting where opioid analgesics were primarily utilized, thus the patient estimates reported in this review can only be generalized to the retail setting of care and may not be applicable to other settings in which opioid analgesics may be prescribed or dispensed, such as mail-order/specialty pharmacies or hospitals and various other clinical settings where patients receive health care.

Of note, there have been changes in the underlying data and methodology of the proprietary database, IQVIA NPA, in part to account for the dynamic pharmaceutical market, including a change to manage prescription claims that are voided and/or reversed. Because TPT patient data are derived from NPA prescription data, projected patient estimates have been adjusted and restated in the database back to January 2017. Data prior to 2017 remain unadjusted. As a result, a trend break occurs between the 2016 and 2017 patient estimates who received prescriptions dispensed from the retail pharmacies (an approximately 2% decrease in the number of dispensed prescriptions for opioid analgesics); any changes over time must be interpreted in the context of the changes in the underlying data and methodology.

According to the U.S. office-based physician surveys, the most common diagnoses associated with the use of analgesics in pediatric patients (0-17 years) in 2018 were for the management of fractures, injuries, and post-operative acute pain conditions (such as management of inguinal hernia). Of note, dentists are not included in the sample of U.S. office-based physician surveys.

The office-based physician surveys database provides reported drug use mentions and diagnoses information to provide insight into prescriber intent. However, estimates below the acceptable count allowable (<100,000) may not provide a reliable national estimate. The diagnoses data were obtained from surveys of a sample of 3,200 office-based physicians with 115 pain specialists reporting on patient activity during one day per month. Although physician survey data provide an insight into the prescriber's intent, they are not directly linked to dispensed prescriptions. Due to the small sample sizes captured with correspondingly large confidence intervals, these data should be interpreted in the context of these limitations and may not be representative of national trends.

5. CONCLUSIONS

In this review, utilization of opioid analgesic dispensed prescriptions was examined in pediatric patients to provide contextual background for the advisory committee meeting discussion. In 2018, an estimated 1.8 million pediatric patients 0-17 years old received dispensed prescriptions for opioid analgesics, a 59% decrease from 2009. Hydrocodone-acetaminophen, codeine-acetaminophen, oxycodone-acetaminophen, single-ingredient oxycodone IR and single-ingredient tramadol were the most frequently dispensed opioid analgesic prescriptions among pediatric patients during the study-period from 2009-2018. The decrease in opioid utilization was primarily driven by decreases in codeine- and hydrocodone-containing products. The use of single-ingredient oxycodone IR in pediatric patients appears to have increased over the study-period. Analysis of dispensed opioid analgesics prescriptions reveals that surgical specialists most frequently prescribed to pediatric patients, followed by primary care physicians and dentists. According to the U.S. office-based physician surveys, opioid analgesics were mainly mentioned to be used for the management of acute conditions, such as fractures, injuries and inguinal hernia.

6. APPENDIX A: TABLES

Table 2. Estimated number of pediatric patients (0-17 years old)* who received dispensed prescriptions for opioid analgesics, from U.S. outpatient retail pharmacies, 2009-2018

	Year 2009		Year 2010		Year 2011		Year 2012		Year 2013	
	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%
Total Patients Dispensed Opioid Analgesics	**65,191,600**	**100.0%**	**66,537,267**	**100.0%**	**69,668,459**	**100.0%**	**68,421,361**	**100.0%**	**65,907,195**	**100.0%**
0-17 years old	**4,224,931**	**6.5%**	**4,210,369**	**6.3%**	**4,116,086**	**5.9%**	**3,763,904**	**5.5%**	**3,299,968**	**5.0%**
Hydrocodone-acetaminophen	1,916,624	45.4%	1,975,582	46.9%	1,997,688	48.5%	1,891,957	50.3%	1,773,354	53.7%
Codeine-acetaminophen	2,159,316	51.1%	2,078,265	49.4%	1,922,235	46.7%	1,648,538	43.8%	1,276,377	38.7%
Oxycodone-acetaminophen	297,453	7.0%	301,283	7.2%	299,559	7.3%	277,372	7.4%	255,554	7.7%
Oxycodone HCL	32,370	0.8%	43,366	1.0%	48,179	1.2%	56,819	1.5%	69,865	2.1%
Tramadol HCL	111,396	2.6%	118,874	2.8%	146,653	3.6%	172,240	4.6%	169,716	5.1%
Meperidine HCL	40,878	1.0%	39,504	0.9%	39,411	1.0%	35,123	0.9%	32,302	1.0%
Tramadol-acetaminophen	11,772	0.3%	10,376	0.2%	10,826	0.3%	9,526	0.3%	8,302	0.3%
Morphine Sulphate	4,955	0.1%	4,685	0.1%	4,824	0.1%	4,885	0.1%	4,857	0.1%
Hydrocodone-Ibuprofen	26,694	0.6%	26,496	0.6%	26,043	0.6%	22,639	0.6%	20,333	0.6%
Hydromorphone HCL	5,520	0.1%	5,465	0.1%	5,708	0.1%	5,255	0.1%	4,455	0.1%
Methadone HCL	1,817	0.0%	1,900	0.0%	1,947	0.0%	1,634	0.0%	1,596	0.0%
Codeine Sulfate	1,697	0.0%	1,536	0.0%	1,580	0.0%	1,352	0.0%	938	0.0%
Fentanyl	1,646	0.0%	2,041	0.0%	1,770	0.0%	1,580	0.0%	1,156	0.0%
Codeine- butalbital-acetaminophen-caffeine	1,545	0.0%	1,405	0.0%	1,562	0.0%	1,504	0.0%	1,550	0.0%
Tapentadol HCL	255	0.0%	908	0.0%	1,440	0.0%	952	0.0%	452	0.0%
Codeine- butalbital-aspirin-caffeine	940	0.0%	792	0.0%	732	0.0%	578	0.0%	541	0.0%
Buprenorphine	--	--	--	--	128	0.0%	128	0.0%	147	0.0%
Dihydrocodeine-acetaminophen-caffeine	415	0.0%	465	0.0%	737	0.0%	368	0.0%	113	0.0%
Oxymorphone HCL	131	0.0%	134	0.0%	151	0.0%	140	0.0%	92	0.0%
Butorphanol Tartrate	230	0.0%	245	0.0%	188	0.0%	225	0.0%	128	0.0%
Pentazocine-naloxone	285	0.0%	384	0.0%	606	0.0%	409	0.0%	340	0.0%
Fentanyl Citrate	65	0.0%	58	0.0%	43	0.0%	13	0.0%	8	0.0%
Hydrocodone Bitartrate	--	--	--	--	--	--	--	--	--	--
Buprenorphine HCL	--	--	--	--	--	--	--	--	--	--
Ooium Tincture	52	0.0%	266	0.0%	118	0.0%	44	0.0%	37	0.0%
Oxycodone-Ibuprofen	630	0.0%	548	0.0%	462	0.0%	340	0.0%	173	0.0%
Morphine-naltrexone	7	0.0%	53	0.0%	13	0.0%	--	--	--	--
Levorphanol Tartrate	7	0.0%	1	0.0%	2	0.0%	1	0.0%	--	--
Morphine Sulfate beads	73	0.0%	39	0.0%	21	0.0%	5	0.0%	4	0.0%
Codeine-aspirin	7	0.0%	6	0.0%	--	--	--	--	--	--
Digydrocodeine-aspirin-caffeine	9	0.0%	--	--	2	0.0%	--	--	1	0.0%
Codeine Phosphate	57	0.0%	21	0.0%	--	--	--	--	--	--
Hydrocodone-aspirin	--	--	1	0.0%	--	--	--	--	--	--
Meperidine-promethazine	1,147	0.0%	57	0.0%	12	0.0%	--	--	--	--
Oxycodone-aspirin	1,033	0.0%	873	0.0%	829	0.0%	588	0.0%	402	0.0%
Pentazocine-acetaminophen	108	0.0%	83	0.0%	113	0.0%	91	0.0%	74	0.0%
18+	**58,826,091**	**90.2%**	**60,620,851**	**91.1%**	**63,835,979**	**91.6%**	**63,278,855**	**92.5%**	**60,554,867**	**91.9%**
Unknown Age	**3,524,826**	**5.4%**	**1,762,137**	**2.6%**	**1,543,919**	**2.2%**	**1,043,968**	**1.5%**	**3,567,991**	**5.4%**

Source: IQVIA Total Patient Tracker™. 2009-2018. Data extracted July 2019. File: TPT Top 5.peds by Age grp.xlsx

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-17 years include patients less than 18 years old (17 years and 11 months).

Table 2 (continued).

	Year 2014		Year 2015		Year 2016		Year 2017		Year 2018	
	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%
Total Patients Dispensed Opioid Analgesics	**64,740,627**	**100.0%**	**62,784,792**	**100.0%**	**62,638,218**	**100.0%**	**56,521,421**	**100.0%**	**50,307,376**	**100.0%**
0-17 years old	**3,024,848**	**4.7%**	**2,566,016**	**4.1%**	**2,684,195**	**4.3%**	**2,236,399**	**4.0%**	**1,750,465**	**3.5%**
Hydrocodone-acetaminophen	1,648,084	54.5%	1,365,890	53.2%	1,403,653	52.3%	1,256,000	56.2%	1,056,914	60.4%
Codeine-acetaminophen	1,075,571	35.6%	1,041,424	40.6%	889,199	33.1%	598,311	26.8%	343,312	19.6%
Oxycodone-acetaminophen	258,425	8.5%	216,740	8.4%	231,526	8.6%	197,679	8.8%	152,798	8.7%
Oxycodone HCL	99,950	3.3%	108,932	4.2%	147,711	5.5%	151,521	6.8%	150,598	8.6%
Tramadol HCL	186,675	6.2%	146,861	5.7%	156,128	5.8%	124,543	5.6%	94,668	5.4%
Meperidine HCL	29,470	1.0%	26,157	1.0%	26,196	1.0%	22,690	1.0%	20,690	1.2%
Tramadol-acetaminophen	8,470	0.3%	8,814	0.3%	8,791	0.3%	7,372	0.3%	6,846	0.4%
Morphine Sulphate	7,111	0.2%	4,423	0.2%	6,217	0.2%	5,878	0.3%	5,469	0.3%
Hydrocodone-Ibuprofen	17,459	0.6%	11,816	0.5%	9,717	0.4%	6,539	0.3%	4,344	0.2%
Hydromorphone HCL	5,533	0.2%	4,306	0.2%	4,302	0.2%	3,551	0.2%	2,926	0.2%
Methadone HCL	2,812	0.1%	1,593	0.1%	1,703	0.1%	1,425	0.1%	1,377	0.1%
Codeine Sulfate	740	0.0%	734	0.0%	812	0.0%	787	0.0%	989	0.1%
Fentanyl	2,180	0.1%	1,127	0.0%	1,205	0.0%	788	0.0%	730	0.0%
Codeine- butalbital-acetaminophen-caffeine	1,704	0.1%	1,300	0.1%	1,229	0.0%	842	0.0%	579	0.0%
Tapentadol HCL	507	0.0%	268	0.0%	320	0.0%	273	0.0%	164	0.0%
Codeine- butalbital-aspirin-caffeine	438	0.0%	257	0.0%	263	0.0%	167	0.0%	143	0.0%
Buprenorphine	231	0.0%	114	0.0%	135	0.0%	98	0.0%	85	0.0%
Dihydrocodeine-acetaminophen-caffeine	15	0.0%	64	0.0%	59	0.0%	84	0.0%	73	0.0%
Oxymorphone HCL	152	0.0%	55	0.0%	70	0.0%	49	0.0%	38	0.0%
Butorphanol Tartrate	191	0.0%	108	0.0%	98	0.0%	57	0.0%	37	0.0%
Pentazocine-naloxone	401	0.0%	235	0.0%	149	0.0%	76	0.0%	36	0.0%
Fentanyl Citrate	8	0.0%	9	0.0%	7	0.0%	5	0.0%	25	0.0%
Hydrocodone Bitartrate	7	0.0%	20	0.0%	27	0.0%	18	0.0%	18	0.0%
Buprenorphine HCL	--	--	--	--	21	0.0%	16	0.0%	15	0.0%
Ooium Tincture	43	0.0%	32	0.0%	31	0.0%	17	0.0%	14	0.0%
Oxycodone-Ibuprofen	85	0.0%	31	0.0%	17	0.0%	11	0.0%	14	0.0%
Morphine-naltrexone			1	0.0%	19	0.0%	17	0.0%	11	0.0%
Levorphanol Tartrate	1	0.0%	4	0.0%	6	0.0%	4	0.0%	3	0.0%
Morphine Sulfate beads	11	0.0%	5	0.0%	6	0.0%	1	0.0%	1	0.0%
Codeine-aspirin	--	--	--	--	--	--	--	--	--	--
Digydrocodeine-aspirin-caffeine	--	--	--	--	--	--	--	--	--	--
Codeine Phosphate	--	--	--	--	--	--	--	--	--	--
Hydrocodone-aspirin	--	--	--	--	--	--	--	--	--	--
Meperidine-promethazine	1	0.0%	--	--	--	--	--	--	--	--
Oxycodone-aspirin	211	0.0%	76	0.0%	18	0.0%	11	0.0%	--	--
Pentazocine-acetaminophen	10	0.0%	--	--	--	--	--	--	--	--
18+	**58,970,689**	**91.1%**	**58,927,981**	**93.9%**	**59,607,237**	**95.2%**	**53,821,747**	**95.2%**	**48,358,547**	**96.1%**
Unknown Age	**2,961,372**	**4.6%**	**957,918**	**1.5%**	**109,643**	**0.2%**	**587,319**	**1.0%**	**131,379**	**0.3%**

Source: IQVIA Total Patient Tracker™. 2009-2018. Data extracted July 2019. File: TPT Top 5.peds by Age grp.xlsx

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-17 years include patients less than 18 years old (17 years and 11 months). The patient estimates are nationally projected based on a sample of prescriptions claims from retail pharmacies and should be interpreted with caution as they are based on a small sample size, particularly for the pediatric population. Certain estimates may be a result of errors such as wrong date of birth on prescriptions; however, medical charts were not available for validation.

Of note, there was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided or reversed. Prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017, data prior to January 2017 have not been adjusted to the new methodology; therefore, the dotted line represents a trend break and any changes over time must be interpreted in the context of the changes in methodology. In 2018, an estimated 2% of total prescription claims for opioid analgesics dispensed from U.S. retail pharmacies appears to have been voided or reversed.

Table 3. Estimated number of pediatric patients (<2, 2-11, 12-17 years old)* who received dispensed prescriptions for top 5 opioid analgesics, from U.S. outpatient retail pharmacies, 2009-2018

	2009		2010		2011		2012		2013	
	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%
Total Patients Dispensed Opioid Analgesics	65,191,600	100.0%	66,537,267	100.0%	69,668,459	100.0%	68,421,361	100.0%	65,907,195	100.0%
0-17 years old	4,224,931	6.5%	4,210,369	6.3%	4,116,086	5.9%	3,763,904	5.5%	3,299,968	5.0%
Hydrocodone-Acetaminophen	1,916,624	45.4%	1,975,582	46.9%	1,997,688	48.5%	1,891,957	50.3%	1,773,354	53.7%
Codeine-Acetaminophen	2,159,316	51.1%	2,078,265	49.4%	1,922,235	46.7%	1,648,538	43.8%	1,276,377	38.7%
Oxycodone-Acetaminophen	297,453	7.0%	301,283	7.2%	299,559	7.3%	277,372	7.4%	255,554	7.7%
Oxycodone IR	31,044	0.7%	42,776	1.0%	47,316	1.1%	56,549	1.5%	70,914	2.1%
Tramadol HCL	111,396	2.6%	118,874	2.8%	146,653	3.6%	172,240	4.6%	169,716	5.1%
<2 year old	109,884	2.6%	106,225	2.5%	95,986	2.3%	82,537	2.2%	59,826	1.8%
Hydrocodone-Acetaminophen	24,129	22.0%	25,170	23.7%	25,538	26.6%	27,612	33.5%	26,726	44.7%
Oxycodone IR	1,351	1.2%	1,772	1.7%	1,813	1.9%	1,986	2.4%	2,381	4.0%
Codeine-Acetaminophen	87,223	79.4%	82,117	77.3%	68,996	71.9%	53,365	64.7%	34,908	58.3%
Tramadol HCL	2,481	2.3%	2,835	2.7%	3,655	3.8%	4,107	5.0%	2,634	4.4%
Morphine Sulfate	452	0.4%	389	0.4%	567	0.6%	505	0.6%	328	0.5%
2-11 years old	1,709,773	40.5%	1,690,775	40.2%	1,641,598	39.9%	1,458,913	38.8%	1,201,577	36.4%
Hydrocodone-Acetaminophen	484,087	28.3%	514,954	30.5%	545,060	33.2%	523,123	35.9%	497,259	41.4%
Codeine-Acetaminophen	1,260,813	73.7%	1,218,229	72.1%	1,121,585	68.3%	942,524	64.6%	697,251	58.0%
Oxycodone IR	10,375	0.6%	13,212	0.8%	13,434	0.8%	18,168	1.2%	27,002	2.2%
Meperidine HCL	28,019	1.6%	27,585	1.6%	28,185	1.7%	26,014	1.8%	25,099	2.1%
Tramadol HCL	13,900	0.8%	15,810	0.9%	18,715	1.1%	26,118	1.8%	20,125	1.7%
12-17 years old	2,406,246	57.0%	2,412,053	57.3%	2,379,481	57.8%	2,223,231	59.1%	2,042,903	61.9%
Hydrocodone-Acetaminophen	1,409,521	58.6%	1,436,511	59.6%	1,427,838	60.0%	1,341,666	60.3%	1,251,381	61.3%
Codeine-Acetaminophen	812,346	33.8%	778,824	32.3%	732,415	30.8%	653,278	29.4%	544,842	26.7%
Oxycodone-Acetaminophen	282,324	11.7%	286,338	11.9%	282,388	11.9%	263,450	11.8%	245,553	12.0%
Tramadol HCL	99,082	4.1%	107,332	4.4%	131,139	5.5%	146,644	6.6%	150,878	7.4%
Oxycodone IR	19,401	0.8%	27,939	1.2%	32,242	1.4%	36,622	1.6%	41,918	2.1%
18+ years	58,826,091	90.2%	60,620,851	91.1%	63,835,979	91.6%	63,278,855	92.5%	60,554,867	91.9%
Unknown Age	3,524,826	5.4%	1,762,137	2.6%	1,543,919	2.2%	1,043,968	1.5%	3,567,991	5.4%

Table 3. (continued)

	2014		2015		2016		2017		2018	
	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%
Total Patients Dispensed Opioid Analgesics	**64,740,627**	***100.0%***	**62,784,792**	***100.0%***	**62,638,218**	***100.0%***	**56,521,421**	***100.0%***	**50,307,376**	***100.0%***
0-17 years old	**3,024,848**	***4.7%***	**2,566,016**	***4.1%***	**2,684,195**	***4.3%***	**2,236,399**	***4.0%***	**1,750,465**	***3.5%***
Hydrocodone-Acetaminophen	1,648,084	*54.5%*	1,365,890	*53.2%*	1,403,653	*52.3%*	1,256,000	*56.2%*	1,056,914	*60.4%*
Codeine-Acetaminophen	1,075,571	*35.6%*	1,041,424	*40.6%*	889,199	*33.1%*	598,311	*26.8%*	343,312	*19.6%*
Oxycodone-Acetaminophen	258,425	8.5%	216,740	*8.4%*	231,526	*8.6%*	197,679	*8.8%*	152,798	*8.7%*
Oxycodone IR	101,296	3.3%	115,395	4.5%	148,957	5.5%	151,437	6.8%	150,183	8.6%
Tramadol HCL	186,675	*6.2%*	146,861	*5.7%*	156,128	*5.8%*	124,543	*5.6%*	94,668	*5.4%*
<2 year old	**59,393**	**2.0%**	**34,432**	***1.3%***	**51,256**	***1.9%***	**41,895**	***1.9%***	**33,043**	***1.9%***
Hydrocodone-Acetaminophen	30,106	*50.7%*	19,736	*57.3%*	26,740	*52.2%*	24,515	*58.5%*	20,609	*62.4%*
Oxycodone IR	4,861	8.2%	4,430	12.9%	7,664	15.0%	7,619	18.2%	7,428	22.5%
Codeine-Acetaminophen	27,484	46.3%	18,883	*54.8%*	14,904	*29.1%*	5,974	*14.3%*	1,842	*5.6%*
Tramadol HCL	3,797	6.4%	1,922	5.6%	2,103	4.1%	1,890	4.5%	1,197	3.6%
Morphine Sulfate	559	*0.9%*	257	*0.7%*	648	*1.3%*	612	*1.5%*	581	*1.8%*
2-11 years old	**1,025,961**	***33.9%***	**783,668**	***30.5%***	**843,528**	***31.4%***	**655,998**	***29.3%***	**453,647**	***25.9%***
Hydrocodone-Acetaminophen	440,520	*42.9%*	338,807	*43.2%*	376,450	*44.6%*	342,731	*52.2%*	283,058	*62.4%*
Codeine-Acetaminophen	558,109	*54.4%*	491,681	*62.7%*	393,725	*46.7%*	224,982	*34.3%*	81,790	*18.0%*
Oxycodone IR	42,095	4.1%	49,749	6.3%	65,880	7.8%	67,059	10.2%	62,941	13.9%
Meperidine HCL	23,279	*2.3%*	21,221	*2.7%*	21,910	*2.6%*	19,628	*3.0%*	18,332	*4.0%*
Tramadol HCL	27,653	*2.7%*	18,896	*2.4%*	19,998	*2.4%*	15,270	*2.3%*	11,809	*2.6%*
12-17 years old	**1,947,673**	***64.4%***	**1,794,930**	***70.0%***	**1,788,966**	***66.6%***	**1,540,112**	***68.9%***	**1,265,007**	***72.3%***
Hydrocodone-Acetaminophen	1,179,265	*60.5%*	1,028,132	*57.3%*	1,000,368	*55.9%*	889,068	*57.7%*	753,522	*59.6%*
Codeine-Acetaminophen	490,869	*25.2%*	531,817	*29.6%*	480,859	*26.9%*	367,630	*23.9%*	259,783	*20.5%*
Oxycodone-Acetaminophen	247,679	*12.7%*	235,654	*13.1%*	232,045	*13.0%*	196,236	*12.7%*	151,491	*12.0%*
Tramadol HCL	158,001	*8.1%*	136,881	*7.6%*	135,453	*7.6%*	107,286	*7.0%*	81,471	*6.4%*
Oxycodone IR	55,110	2.8%	62,670	3.5%	75,404	4.2%	76,945	5.0%	80,053	6.3%
18+ years	**58,970,689**	***91.1%***	**58,927,981**	***93.9%***	**59,607,237**	***95.2%***	**53,821,747**	***95.2%***	**48,358,547**	***96.1%***
Unknown Age	**2,961,372**	***4.6%***	**957,918**	***1.5%***	**109,643**	***0.2%***	**587,319**	***1.0%***	**131,379**	***0.3%***

Source: IQVIA Total Patient Tracker™. 2009-2018. Data extracted July 2019. File: TPT Top 5.peds by Age grp.xlsx
Of note, there was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided and/or reversed. Because TPT patient data are derived from NPA prescription data, projected patient estimates have been adjusted and restated in the database back to January 2017, data prior to 2017 remain unadjusted. As a result, a trend break occurs between the 2016 and 2017 patient estimates who received prescriptions dispensed from the retail pharmacies; any changes over time must be interpreted in the context of the changes in the underlying data and methodology. In 2018, an estimated 3% of total prescription claims for codeine-containing products dispensed from U.S. retail pharmacies appeared to have been voided or reversed. Data are inclusive of all indications. The patient estimates are nationally projected based on a sample of prescriptions claims from retail pharmacies and should be interpreted with caution as they are based on a small sample size, particularly for the pediatric population. Certain estimates may be a result of errors such as wrong date of birth on prescriptions; however, medical charts were not available for validation. Summarization of these projected estimates across patient age groups, time periods, and/or products may lead to differences in patient counts due to rounding attributable to the projection methodology utilized as well as double counting of patients across age groups and time as patients aged over time.
*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-17 years include patients less than 18 years old (17 years and 11 months).

Table 4. Top prescriber specialties based on estimated number of opioid analgesic prescriptions* dispensed from U.S. outpatient retail pharmacies to pediatric patients (<2, 2-11, 2-17 years old) in 2018.

	2018	
	TRxs	**%**
Total Prescriptions Dispensed for Opioid Analgesics	**168,222,064**	***100.0%***
0-17 years	**2,090,372**	***1.2%***
0-1 year old	**35,835**	***1.7%***
Urology	11,028	*30.8%*
Surgical Specialties	5,324	*14.9%*
NP/PA	4,052	*11.3%*
Pediatrics	3,076	*8.6%*
Emergency Medicine	1,929	*5.4%*
Otolaryngology	1,438	*4.0%*
FP/GP/IM	1,409	*3.9%*
Dentistry	470	*1.3%*
Specialty Unspecified	5,637	*15.7%*
All Other Specialties	1,472	*4.1%*
2-11 years old	**527,404**	***25.2%***
Otolaryngology	136,368	*25.9%*
Surgical Specialties	92,225	*17.5%*
Dentistry	64,772	*12.3%*
NP/PA	52,605	*10.0%*
Emergency Medicine	40,878	*7.8%*
Pediatrics	28,375	*5.4%*
Urology	23,611	*4.5%*
FP/GP/IM	20,259	*3.8%*
Specialty Unspecified	44,479	*8.4%*
All Other Specialties	23,832	*4.5%*
12-17 years old	**1,527,134**	***73.1%***
Surgical Specialties	696,375	*45.6%*
Dentistry	248,611	*16.3%*
NP/PA	149,543	*9.8%*
Emergency Medicine	95,094	*6.2%*
Otolaryngology	70,995	*4.6%*
FP/GP/IM	64,412	*4.2%*
Pediatrics	41,414	*2.7%*
Podiatry	24,181	*1.6%*
Specialty Unspecified	61,135	*4.0%*
All Other Specialties	75,375	*4.9%*
18+ years	**165,815,291**	***98.6%***
Unknown Age	**316,400**	***0.2%***

*Source: IQVIA National Prescription Audit™. 2019. Data extracted June 2019. File: NPA Adhoc copy of Opioid Analgesic Specialties 2018.xlsx
**FP/GP/IM-family practice, general practice and internal medicine, NP/PA- nurse practitioners/physician assistants, Pediatrics-Pediatrics, internal medicine pediatrics and critical care pediatrics, Surgical Specialties-cardiothoracic surgery, general surgery, neurological surgery, orthopedic surgery of the spine, orthopedic surgery, pediatric neuro surgery, plastic surgery, thoracic surgery, critical care Surgery, colon and rectal surgery, cardiovascular surgery and other surgical specialties.

Table 5. Top diagnoses* associated with the use of opioid analgesics in pediatric patients (<2, 2-11, 12-17 years old) as reported by U.S. office-based physician surveys, 2018.

	2018			
	Uses N (000)	Share %	95% Confidence Interval (000)	
TOTAL USES (Non Injectable Opioid Analgesics)	**54,818**	**100.0%**	**53,352**	**56,285**
Patients (0-17 years old)	**1,879**	**3.4%**	**1,608**	**2,151**
Fracture and Injuries	990	52.7%	793	1,187
K40 Inguinal hernia	142	7.6%	68	217
M41 Scoliosis	81	4.3%	24	137
M25 Other joint disorder, not elsewhere classified	56	3.0%	9	103
Z47 Orthopedic aftercare	41	2.2%	1	81
All Others	569	30.3%	420	719
0-1 year old	**61**	**0.1%**	**12**	**109**
Fractures and Injuries	38	62.5%	0	76
M79 Oth and unsp soft tissue disorders, not elsewhere classified	23	37.5%	0	53
2-11 years old	**855**	**1.6%**	**672**	**1,038**
Fractures and Injuries	646	75.6%	487	805
K40 Inguinal hernia	107	12.5%	42	171
L02 Cutaneous abscess, furuncle and carbuncle	30	3.5%	0	64
H66 Suppurative and unspecified otitis media	19	2.3%	0	47
G12 Spinal muscular atrophy and related syndromes	19	2.2%	0	46
All Others	34	4.0%	0	71
12-17 years old	**963**	**1.8%**	**769**	**1,158**
Fractures and Injuries	306	31.8%	196	415
M41 Scoliosis	81	8.4%	24	137
M25 Other joint disorder, not elsewhere classified	56	5.8%	9	103
Z47 Orthopedic aftercare	41	4.3%	1	81
K35 Acute appendicitis	38	4.0%	0	77
All Others	441	45.8%	310	573
18 years or older	**51,904**	**94.7%**	**50,477**	**53,331**
Unpecified Age	**1,035**	**1.9%**	**833**	**1,236**

Source: Syneos Health Research & Insights LLC., TreatmentAnswers™. 2018. Data extracted July 2019. File: PDDA_OA_Opana_age_ICD10_dx3_Top5_2.&-23-2019.xls
*Diagnosis data are not directly linked to dispensed prescriptions but are obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity during one day per month. Because of the small sample sizes with correspondingly large confidence intervals, the drug use mentions <100,000 are too low to provide reliable national estimates for the diagnoses and therefore, preclude meaningful interpretation of data trends.
Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-17 years include patients less than 18 years old (17 years and 11 months).

7. APPENDIX B: DATABASE DESCRIPTIONS

IQVIA National Sales Perspectives™ (NSP)

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

The manufacturer sales distribution data do not provide an estimate of direct patient use but do provide a national estimate of units sold from the manufacturer to various retail and non-retail settings of care. The amount of product purchased by these settings of care may be a possible surrogate for use if we assume that facilities purchase drugs in quantities reflective of actual patient use.

IQVIA Total Patient Tracker™ (TPT)

IQVIA Total Patient Tracker (TPT) is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from U.S. retail pharmacies. TPT uses prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients and multiple prescription fills, producing quick and reliable unique patient counts. IQVIA has 92% coverage and a sample of approximately 58,900 retail pharmacies. IQVIA captures about 3.8 billion transactions annually. TPT is projected to the known universe of retail pharmacies. Due to the changing pharmaceutical marketplace, IQVIA has implemented changes to its prescription database, National Prescription Audit™ (NPA), to manage prescription voids, reversals, and abandonments that span multiple weeks. Beginning in January 2019, IQVIA has projected published prescription volumes dispensed from the retail pharmacies based on sold date, instead of date of adjudication (i.e., fill date). Because TPT patient data are derived from NPA prescription data, projected patient estimates have been adjusted and restated in the database back to January 2017, data prior to 2017 remain unadjusted. As a result, a trend break occurs between 2016 and 2017 patient estimates who received prescriptions dispensed from the retail pharmacies; any changes over time must be interpreted in the context of the changes in the underlying data and methodology.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

Of note, the estimated prescription and/or patient counts provided are based on projections of sample prescription claims data and therefore have some degree of inherent sampling error. These estimates are not intended to be representations of exact enumerations and should be interpreted with caution particularly if they are based on a small sample size. In addition, the data cannot be validated due to lack of access to medical records in the data sources.

IQVIA National Prescription Audit™ (NPA)

The IQVIA National Prescription Audit (NPA) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.7 billion prescription claims per year, captured from a sample of the universe of approximately 58,900 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 92% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 60 – 86% (varies by class and geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

Due to the changing pharmaceutical marketplace, IQVIA has implemented changes to its prescription database to manage prescription voids, reversals, and abandonments that span multiple weeks. Beginning in January 2019, IQVIA has projected published prescription volumes dispensed from the retail pharmacies based on sold date, instead of date of adjudication (i.e., fill date). Projected estimates have been adjusted and restated in the database back to January 2017, data prior to 2017 remain unadjusted. As a result, a trend break occurs between 2016 and 2017 prescription volumes dispensed from the retail pharmacies, any changes over time must be interpreted in the context of the changes in the underlying data and methodology.

Dispensed prescription estimates are nationally projected based on a sample of prescriptions claims from mail-order/specialty and retail pharmacies. Summarization of these projected estimates across time periods and/or settings of care may lead to differences in prescription count due to rounding attributable to the projection methodology utilized. No statistical tests were performed on these estimates to determine statistically significant changes over time. Therefore, all changes over time should be considered approximate, and may be due to random error.

Syneos Health Research & Insights LLC., TreatmentAnswers™ with Pain Panel

Syneos Health Research & Insights, LLC., TreatmentAnswers™ is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology Review

Date:	September 3, 2019
Reviewer:	Christina R. Greene, Ph.D. *Epidemiologist* Division of Epidemiology II
Secondary Reviewer:	Rose Radin, Ph.D., M.P.H. *Team Lead, Drug Abuse Team 2* Division of Epidemiology II
Tertiary Reviewer:	Jana McAninch, M.D., M.P.H., M.S. *Senior Medical Epidemiologist* Division of Epidemiology II
Subject:	Prescription Opioid Abuse and Related Outcomes in the Pediatric Population
Drug Name(s):	Opioid Analgesics
Application Type/Number:	Multiple
Applicant/Sponsor:	Multiple
OSE RCM #:	2018-2034

TABLE OF CONTENTS

ABBREVIATIONS

AAPCC: American Association of Poison Control Centers
AC: Advisory Committee
AD: Abuse-Deterrent
CDC: Centers for Disease Control and Prevention
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ED: Emergency Department
FDA: U.S. Food and Drug Administration
ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision
MTF: Monitoring the Future
NDA: New Drug Application
NEISS-CADES: National Electronic Injury Surveillance System -- Cooperative Adverse Drug Event Surveillance
NMUPO: Nonmedical Use of Prescription Opioids
NPDS: National Poison Data System
NSDUH: National Survey on Drug Use and Health
OA: Opioid Analgesic
OUD: Opioid Use Disorder
PCC: Poison Control Center
PMR: Postmarketing Requirement
PO: Prescription Opioids
Rx: Prescription
SSLS: Secondary Student Life Survey
SUD: Substance Use Disorder
U.S.: United States

EXECUTIVE SUMMARY

On September 26, 2019, the Pediatric Advisory Committee and the Drug Safety and Risk Management Advisory Committee will meet to discuss the pediatric-focused safety review for OxyContin (oxycodone hydrochloride) extended-release tablets, as mandated by the Food and Drug Administration (FDA) Safety and Innovation Act, and to discuss pediatric data considerations for opioid analgesic labeling. For all regulatory questions involving opioids, FDA considers the potential broader public health implications, including potential harms associated with misuse and abuse of the drugs by patients or others in the community. To inform this consideration and discussion at the upcoming advisory committee meeting, the Division of Epidemiology II (DEPI) provides recent data on prescription opioid misuse and abuse in pediatric populations as well as a review of the epidemiologic literature examining opioid analgesic misuse, abuse, addiction, and overdose in children and adolescents and the risk of these adverse outcomes following opioid analgesic therapy in these populations.

National surveys, including the National Survey on Drug Use and Health (NSDUH) and the Monitoring the Future (MTF) survey, indicate that adolescent prescription opioid misuse and abuse have been declining in recent years, with the most recent data estimating that approximately 3-4% of adolescents have misused or abused prescription opioids in the past year. Among adolescents who misuse or abuse prescription opioids, most received them from a friend or relative, although nearly a third obtained them via their own prescription (1-3). Additionally, adolescents perceive prescription opioids as becoming more difficult to obtain for misuse and abuse compared to previous years (3).

In 2016 and 2017 in the U.S., an estimated 4.1% of emergency department (ED) visits due to adverse events from prescription opioids occurred in patients less than 18 years old (4). The rate of ED visits due to nonmedical use* of prescription opioids is lower among adolescents aged 12-17 than among adults aged 18 or older. Among adolescents, ED visits due to self-harm involving prescription opioids occur at slightly higher rates than visits due to nonmedical prescription opioid use, with annual estimates of 2,130 and 2,617 visits due to nonmedical use[*] and self-harm, respectively (4).

Based on data from the U.S. poison control centers in 2000 to 2015, most opioid-related poison control center exposure calls involved children ages 5 years and younger; however, prescription opioid exposure calls in adolescents were more likely to involve misuse/abuse or suicide attempts and to result in serious adverse outcomes (5). From 2000-2015, calls involving intentional prescription opioid exposures in adolescents increased from 2000-2009 and then declined from 2009-2015, whereas calls involving adolescent suicide attempts, specifically, increased 52% over the entire study period.

[*] Here, nonmedical use includes abuse of a medication, therapeutic misuse (use other than as directed by a clinician), and overdoses without indication of intent.

Limited evidence from the published literature suggests that medical use of prescription opioids may place adolescents at a modestly increased risk of future opioid misuse or abuse. Medical use of prescription opioids is associated with double the risk of misuse in later adolescence (6,7,8,12) and 1.3 to 1.7 times higher risk of misuse in early adulthood (9,10). However, this association could be due, at least in part, to unmeasured factors—such as the reason for opioid use (e.g. injury), ongoing pain, use of other substances, and other psychosocial factors—associated with both medical use of opioids and future risk of misuse or abuse (29,30). Longitudinal data suggest that opioid misuse and abuse during adolescence are associated with substance use disorders (SUDs) in adulthood; however, medical opioid use alone in adolescence does not appear to increase the risk of SUD in adulthood. (11, 12). Because data are scarce on the risks of SUD and other serious outcomes, such as overdose, following medical use of opioid analgesics in children and adolescents (11-13, 31), more research is needed to better understand these relationships while fully accounting for potential confounding factors.

1 INTRODUCTION AND REGULATORY HISTORY

Opioids were involved in 47,600 overdose deaths in the U.S. in 2017, 35% of which involved a prescription opioid (15,16). Of these,1.2% were in children less than 18 years of age (16). The pediatric mortality rate due to prescription opioid poisoning increased by 131% from 1999-2016 (17). FDA seeks to better understand and mitigate the risks posed to pediatric populations from prescription opioids, while ensuring the availability of these medications for children and adolescents who need them. Adolescents' ongoing brain development makes them particularly vulnerable to developing addictive disorders when exposed to substances such as alcohol or marijuana (34), and there is a need to better understand the risks associated with exposure to prescription opioids in this population. On August 13, 2015, FDA made its first approval of a long-acting opioid analgesic for pediatric patients, a supplement to the label for OxyContin® (oxycodone hydrochloride) for use in selected patients aged 11 to 17 years.[†] Because physicians could already prescribe oxycodone and most other approved opioid analgesics to pediatric patients per their clinical judgment, the approval aimed to provide prescribers with evidence-based dosing information for pediatric patients.

This regulatory action underscored the need for a better understanding of the risks of serious adverse outcomes associated with opioid analgesic use in pediatric populations. Therefore, on September 15, 2016, FDA held an advisory committee (AC) to discuss appropriate development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients.[‡] The Division of Epidemiology (DEPI) was consulted to assess the epidemiologic literature examining misuse, abuse, addiction, overdose, and death in pediatric populations prescribed opioid analgesics. A central concern of this AC was whether legitimate medical use of opioid analgesics increased a young person's risk for subsequent misuse, abuse, or other opioid-related adverse outcomes. However, the review found a paucity of literature that examined adverse

[‡] Federal Register notice at https://www.federalregister.gov/documents/2016/08/17/2016-19589/pediatric-advisory-committee-notice-of-meeting-establishment-of-a-public-docket-request-for-comments, accessed 7/30/2019.

outcomes following legitimate medical use of opioids in adolescents. The one longitudinal study that examined this association reported that adolescent use of an opioid for medical purposes was associated with a 33% increased risk of future misuse or abuse of opioid analgesics. Additionally, the review identified no longitudinal studies of the risk of substance use disorder (SUD) or other opioid-related adverse outcomes following legitimate medical use of opioid analgesics in pediatric patients.

The FDA has convened a joint meeting of the Pediatric Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the pediatric-focused safety review for OxyContin extended-release tablets and to discuss pediatric data considerations for opioid analgesics labeling (docket number FDA-2019-N-3617).[§] To provide context for this discussion, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted DEPI to review the epidemiologic literature, as well as national data sources to address the following questions:

- Describe the occurrence of prescription opioid misuse, abuse, and related morbidity in the pediatric population, as well as contextual information such as self-reported source and ease of obtaining drugs for misuse and abuse.
- Evaluate the available epidemiologic literature examining misuse, abuse, addiction, overdose, and death in pediatric populations who are legitimately prescribed opioid analgesics for acute pain.

The goal of this review is to provide an updated assessment of the epidemiologic evidence on the risks of prescription opioid misuse, abuse, addiction, overdose, and death in pediatric populations.

2 REVIEW METHODS AND MATERIALS

2.1 OVERVIEW AND FRAMEWORK

We reviewed several data sources to describe the misuse/abuse of opioids in pediatric populations, generally defined as age less than 18 years, except where noted. The framework used to summarize findings from these data sources is outlined in **Table 1**, with a more detailed description of the methods in **Sections 2.2 through 2.6**. Standard FDA regulatory definitions of misuse and abuse (18,19,20) were applied throughout this review, unless otherwise indicated.

Misuse refers to the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse.

Abuse: the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect.

[§] Federal Register notice at https://www.federalregister.gov/documents/2019/08/21/2019-17997/joint-pediatric-advisory-committee-and-drug-safety-and-risk-management-advisory-committee-notice-of

Table 1. Overview of Data Sources to Assess the Current Landscape of Prescription Opioid Analgesic Misuse/Abuse

Statistics assessed	Data sources used	Purpose of assessment
National estimates of reported past-year misuse and abuse	National Survey on Drug Use and Health (NSDUH), 2015-2017	Estimate annual U.S. number and prevalence of self-reported, past-year misuse/abuse of prescription opioid analgesics, within age categories defined by the study: 12-17 years, ≥18 years
National estimates of reported nonmedical use of prescription opioids among adolescents	Monitoring the Future (MTF), 2016-2018	Estimate number of high school seniors reporting misuse/abuse of narcotics (excluding heroin) within the past year
Estimates of morbidity related to nonmedical use of prescription opioids, among people who seek emergency care	National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES), 2016-2017	Estimate number of emergency department (ED) visits for adverse events resulting from nonmedical use of prescription opioid analgesics
Estimates of morbidity and mortality related to misuse/abuse, among people who seek medical care	Published scientific report of National Poison Data System (NPDS) exposure calls to Poison Control Centers (PCCs), 2000-2015 (5)	Calls to PCCs, by Active Pharmaceutical Ingredient (API), reason for exposure, formulation, level of care received, and medical outcome

We also searched the epidemiology literature to determine the risk of future adverse outcomes based on exposure to medical use of prescription opioids in adolescence.

2.2 NATIONAL SURVEY OF DRUG USE AND HEALTH (NSDUH)

Data Source

NSDUH is an annual, federally-funded survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA) designed to provide nationally representative estimates of illicit as well as prescription drug misuse/abuse in the general U.S. population. Strengths of this data source include an in-person survey, and a predominantly stable survey design in recent years with the ability to assess temporal changes in drug misuse/abuse in the general U.S. population.

NSDUH uses a multistage probability sample design to provide annual, nationally-representative estimates for non-institutionalized residents of the United States who are aged 12 years and older. Population subgroups not covered by the survey include individuals residing within institutional facilities (e.g., jails, nursing homes), as well as those without a permanent address (e.g., homeless individuals). The survey is conducted in a face-to-face manner, and during the year 2017, the interview response rate of 50.4% included 68,032 completed interviews. In 2015, NSDUH began eliciting more detailed data on use and misuse/abuse of specific prescription opioid analgesics. Participants are

asked whether they used prescription opioid analgesics in the past year for any reason, and participants who indicate past-year use are then asked about misuse.
NSDUH defines *misuse* of a drug as the following: "use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told" (21). Since NSDUH's definition of misuse includes intentional, non-therapeutic use of a drug to obtain a desired psychological or physiological effect (i.e., abuse), this review labels it *misuse/abuse*. NSDUH defines "any use of pain relievers" as any use of pain relievers for any reason, either use of one's own prescription pain reliever as directed by a physician, or misuse/abuse.

Search Strategy and Analysis
We extracted data from the 2017 survey that related to misuse/abuse of prescription opioids overall and by API. National estimates of misuse/abuse were stratified into two categories based on respondent age, adolescent (ages 12 to 17) or adult (ages 18 and older). We reported the distribution of endorsements for the main source for obtaining the prescription opioid that had been misused/abused most recently. The estimated values reported were: the numbers of individuals in thousands, percent of the total population, and percent of misuse/abuse among those who reported any use in the past-year. Statistically significant changes in numbers or percentages were noted.

2.3 MONITORING THE FUTURE

Data Source
Monitoring the Future (MTF) is an annual survey that examines drug use and related attitudes among America's high school students, college students, and adults through age 55 (22). MTF is composed of three sub-studies, and the components that assess misuse and abuse of opioid analgesics are an annual survey of high school seniors since 1975 and ongoing longitudinal studies of representative samples from high school seniors that have been conducted by mail since 1976. The annual survey is a self-administered, paper-based, machine-readable questionnaire completed during school hours. In 2018, approximately 14,500 students in the 12th grade were surveyed. Additionally, approximately 2,450 high school seniors are surveyed longitudinally on a biennial basis. To secure a nationally representative sample of high school seniors, the survey uses a three-stage sampling procedure, sampling geographic regions, schools, and individual students (23). Sampling weights are employed to calculate national estimates (23). Students are surveyed on nonmedical use (NMU; using the drugs without a doctor's order to do so) of "non-heroin narcotics" (i.e., prescription opioids) in the past year, as well as perceived risk, disapproval, and perceived availability and potential sources for misused narcotics. As MTF's definition of NMU includes intentional, non-therapeutic use of a drug to obtain a desired psychological or physiological effect (i.e., abuse), this review labels it *misuse/abuse*. Nonmedical use of prescription opioids is reported overall and separately for Oxycontin and Vicodin.

Search Strategy and Analysis
We extracted information on misuse/abuse of non-heroin narcotics, perceived ease of availability of non-heroin narcotics, and reported source from which narcotic was acquired from Monitoring the Future in two separate sources, "National Adolescent Drug

Trends" (2) and "National survey results on drug use, 1975-2018: Volume I" (3). Percent of high school seniors reporting misuse/abuse of prescription narcotics and "fairly easy" availability of these substances was reported for the period of 2010 to 2018. Information on the source(s) from which the prescription narcotic was acquired among high school seniors who misused these substances was reported for 2017 and 2018.

2.4 NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM—COOPERATIVE ADVERSE DRUG EVENT SURVEILLANCE (NEISS-CADES)

Data Source

Cases and national estimates of the number of emergency department (ED) visits for drug-related adverse events were based on data from the NEISS-CADES project, a national stratified probability sample of approximately 60 hospitals with a minimum of six beds and a 24-hour ED in the United States and its territories. The NEISS-CADES project, which has been described in detail elsewhere (24-27), is a joint effort of the Centers for Disease Control and Prevention (CDC), the US Consumer Product Safety Commission, and the US Food and Drug Administration. In brief, trained data abstractors located at each participating hospital review clinical records of every ED visit to identify clinician-diagnosed drug related adverse events attributed to medications used for any reason. Abstractors record up to four medications implicated in each adverse event, and narrative descriptions of the incident (including intent of drug use, clinical diagnoses and manifestations). To allow calculation of national estimates, each NEISS-CADES case is assigned a sample weight derived from the inverse probability of selection, adjusted for nonresponse and post-stratified to adjust for the number of annual hospital ED visits.

Search Strategy and Analysis

Staff from the CDC Division of Healthcare Quality Promotion extracted and analyzed NEISS-CADES data from 2016 and 2017 to identify ED visits due to adverse events from prescription opioids. Cases attributed to opioid-containing cough medications were excluded. Numbers of cases and average annual national estimates were tabulated and stratified by age group (0-11 years old, 12-17 years, 18 years and older), and intent of drug use. Clinicians' assessment of patients' intent was categorized as follows:

- Therapeutic use: includes adverse events from therapeutic use (e.g., adverse effects, allergic reactions, medication errors, and unsupervised ingestions by children).
- Self-harm: includes administration of medications to injure or kill oneself.
- Nonmedical use: includes *abuse* of a medication, *therapeutic misuse* (use other than as directed by a clinician), and *opioid overdoses without indication of intent*.

We then estimated population rates using the average annual estimate of opioid-related visits per age group as the numerator and using the average population estimate for 2016-2017 for each age group as the denominator, based on US Census population estimates (28). We also reported a 95% confidence interval (CI) for the calculated rate based on variability of numerator estimates in each age group.

2.5 POISON CONTROL CENTER CALLS FOR PRESCRIPTION OPIOID EXPOSURES IN CHILDREN AND ADOLESCENTS IN THE UNITED STATES: 2000-2015

Data Source

We relied on a published study by Allen et al. (5) titled "Prescription Opioid Exposures Among Children and Adolescents in the United States: 2000-2015" to estimate the burden of prescription opioid exposures that resulted in calls to poison control centers (PCCs) among U.S. children and adolescents under the age of 20 years from 2000-2015. This study was identified in our literature search, which is described in greater detail in Section 2.6.

The American Association of Poison Control Centers (AAPCC) manages the NPDS database, which includes data from all poison control centers in the U.S. and territories on calls from individuals, healthcare professionals, and other interested persons regarding the exposures to prescription drugs, over-the-counter medications, unapproved products, and all other substances. Trained medical personnel field the calls and enter detailed, product-specific information regarding the circumstances of the exposure and its medical management, using a standard data collection procedure. Documentation of calls includes detail on the drug(s), patient characteristics, route of exposure, reported reasons for exposure, level of care received (e.g. admitted to critical care unit vs. treated and released), medical outcomes (e.g. death, no effect) and other more curated variables, such as "relatedness" requiring manual chart review to determine the relatedness of the reported exposure to the outcomes of interest. Reasons for exposure are categorized into groups by AAPCC, and include such categories as "intentional", "unintentional," the former encompassing the subgroups of intentional misuse, abuse, suspected suicide or unknown intent. Additional detail regarding the categories of reasons for exposure is provided in Section 7.1 of this review, and additional detail regarding the categories of medical outcomes is provided in Section 7.2 of this review.

Search Strategy and Analysis

From the published article by Allen et al. (5), we reported on the statistics and figures we considered relevant to understanding the landscape of adverse outcomes related to prescription opioids in the national pediatric population. We reported on statistics included on the reasons for opioid exposure, type of opioid identified, formulation of substance, level of care received, and medical outcome as reported by the NPDS by age categories (0-5 years, 6-12 years, and 13-19 years).

2.6 REVIEW OF THE EPIDEMIOLOGIC LITERATURE ON RISK OF ADVERSE OUTCOMES FOLLOWING PRESCRIPTION OPIOID THERAPY IN PEDIATRIC POPULATIONS

Data Source

We searched PubMed and other sources of articles for peer-reviewed epidemiological studies in the biomedical literature published from January 2009 to June 2019 that examined adverse opioid analgesic-related outcomes in persons under 21 years. We also augmented our search through searching and reviewing newer articles that cited key studies in this field of work. We excluded case studies, reviews, letters, editorials, animal

studies, pharmacokinetic/pharmacodynamic studies, and commentaries. Article abstracts were reviewed for possible inclusion, with a more detailed text analysis guiding final study selection.

Search Strategy and Analysis
We conducted a search of the National Library of Medicine's PubMed database on July 1, 2019 to identify studies that examined the association of medical or therapeutic opioid use and future risk of adverse outcomes. We defined "adverse outcomes" as nonmedical use, misuse, abuse, addiction, overdose or death due to opioid analgesic use. A detailed description of the search string used is available in Section 7.4 of this review.
Our search string yielded 62 articles which were then reviewed for inclusion. Our primary reviewer screened article titles, abstracts, and full articles for inclusion or exclusion. To augment our literature search we also identified articles that cited key studies relevant to our question. Articles were screened based on the following criteria:

1) Measure of medical or therapeutic prescription opioid use in childhood or adolescence
2) Adverse opioid-related outcome – i.e., misuse, abuse, or addiction - following medical opioid use
3) Report of medical prescription opioid use precedes report of adverse related outcome
4) Opioid not prescribed for a complex, chronic indication, e.g. sickle cell disease or cancer, in whom the clinical decision-making about risks of opioid analgesics may differ from the context of acute pain.

Our final review yielded a total of ten articles we considered relevant to understanding the risk of adverse outcomes following medical or therapeutic exposure to opioids in childhood. A further description of all studies included in the literature is detailed in Section 7.5 of this review. The results describe the findings of key studies that were determined to be of greatest relevance to our investigation. We also mentioned and discussed the results of two other studies that examined nonmedical use in pediatric populations as a risk factor for more severe future adverse outcomes.

3 REVIEW RESULTS

3.1 NATIONAL SURVEY ON DRUG USE AND HEALTH (NSDUH)

During 2017, over 90 million individuals in the general U.S. population were estimated to have used prescription opioid analgesics during the previous year for any reason. Over 11 million, or 4.1% of the total population, were estimated to have misused or abused them.[**]

[**] As a reminder, misuse/abuse refers to NSDUH's definition of *misuse:* as "use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told."

In 2017, the top three most frequently misused/abused opioid analgesic products in the general population were hydrocodone, oxycodone and codeine, with estimated misuse/abuse in 6.3 million, 3.7 million and 2.8 million individuals, respectively (Table 3). The prescription opioids with the highest proportion of past-year misuse/abuse out of any past-year use were oxymorphone, buprenorphine, and methadone, respectively misused or abused by 36.2%, 31.7% and 19.5% of individuals who reported any past-year use of each opioid (Table 3).

Table 3. National Survey on Drug Use and Health, 2017: Reported past year use and misuse/abuse of prescription opioids, by active ingredients, individuals aged 12 and older

Active Pharmaceutical Ingredient	Past-Year Any Use (thousands)	Past-Year Misuse/Abuse (thousands)	Misuse/Abuse in Total Population (%)	Misuse/Abuse in Past-Year Any Users (%)
Any	90,799	11,077	4.1	12.2
Hydrocodone	51,979*	6,262*	2.3*	12.0
Oxycodone	26,720	3,735	1.4	14.0
Tramadol	18,485	1,753	0.6	9.5
Codeine	26,870	2,832	1.0	10.5
Morphine	6,231	501	0.2	8.0
Fentanyl***	2,046	245	0.1	12.0
Buprenorphine	2,414	766	0.3	31.7
Oxymorphone	917	332	0.1	36.2
Demerol®	1,202	116	0.0	9.6
Hydromorphone	1,941	244	0.1	12.6
Methadone	1,341	261	0.1	19.5
Other	24,220	966*	0.4*	4.0*

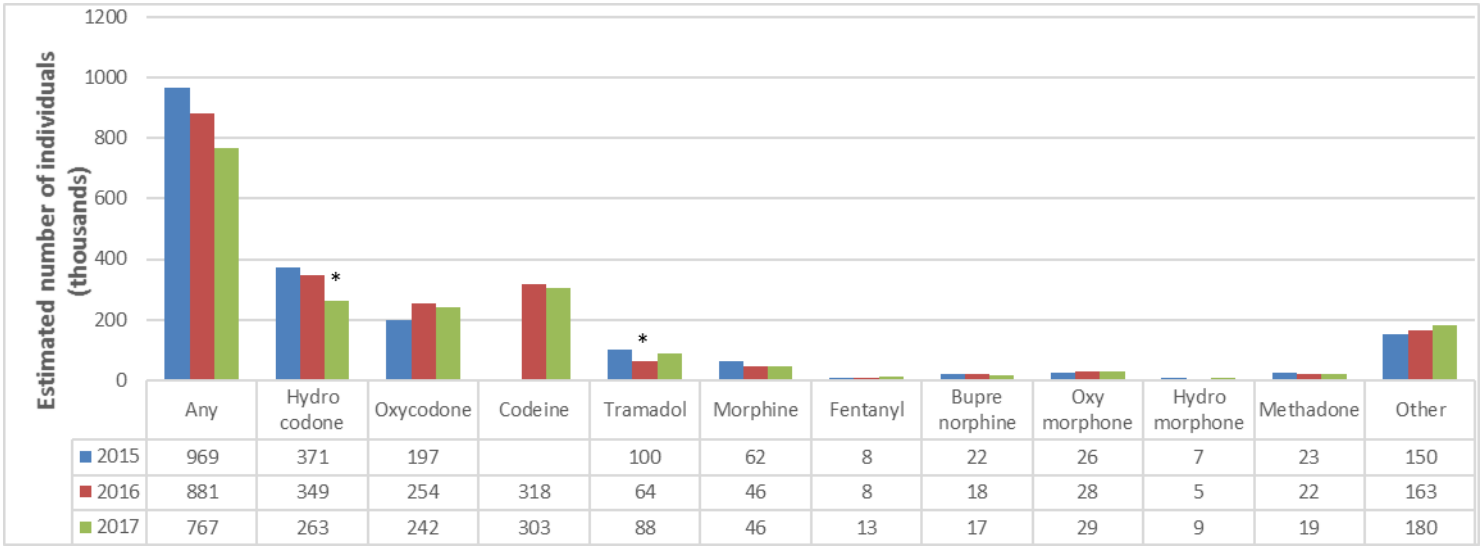
*represent statistically significant changes relative to 2016
***estimate does not include illicit fentanyl

Source: SAMHSA detailed tables, Tables 1.97A-B Available from: https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.pdf
Accessed on 4/20/2019. Note: NSDUH defines misuse of a drug as the following: "use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told"

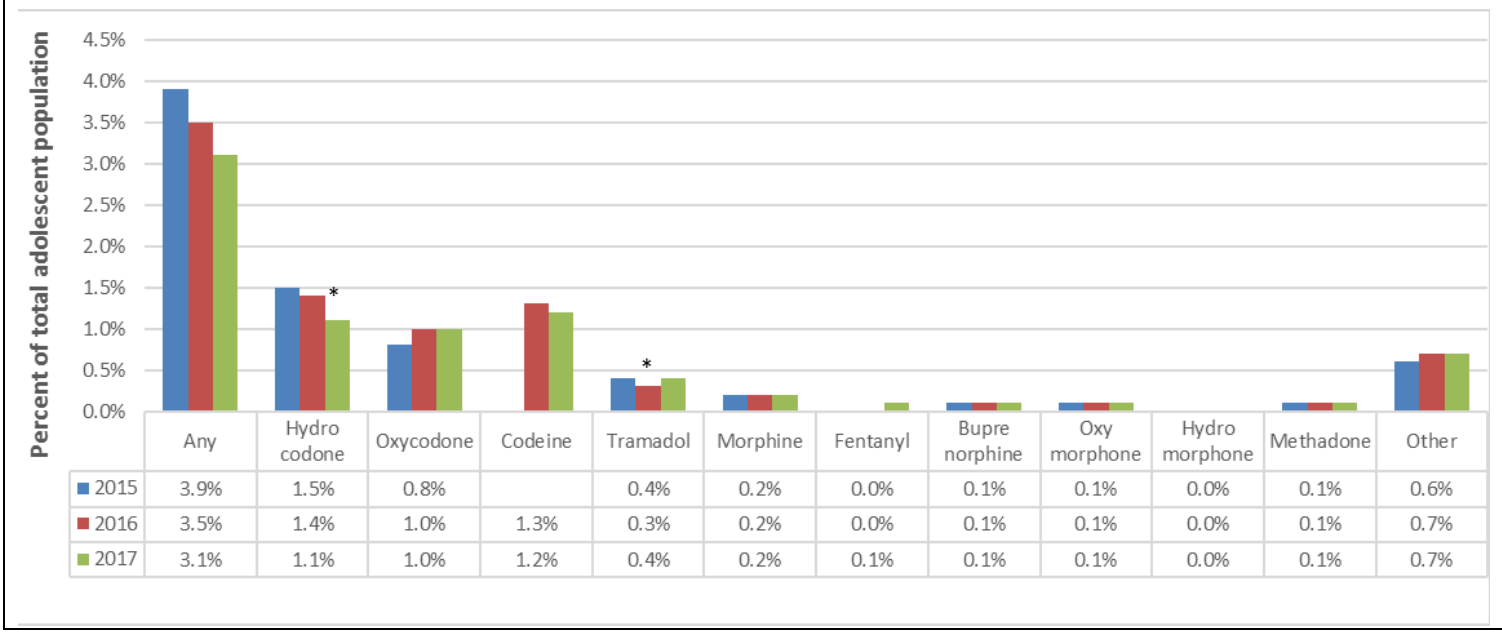
In 2017, 4.3 million adolescents between 12 to 17 years of age were estimated to have used an opioid product in the past year for any reason. An estimated 3.1% of all adolescents misused or abused an opioid over the past year. Hydrocodone, oxycodone, and codeine were the opioid products that were most commonly misused or abused in the adolescent population, with estimated misuse/abuse in 1.1%, 1.0%, and 1.2% of adolescents, respectively (Table 4; Figure 1).

The estimated percent of adolescents engaging in prescription opioid misuse/abuse declined from 2015 to 2017, from an estimated 3.9% to 3.1% of the adolescent population (Figure 1). While the estimated rate of misuse of hydrocodone declined significantly among adults from 2016 to 2017, the oxycodone misuse rate remained relatively stable in the adolescent population over the same period (Figure 1).

Figure 1.
Past-year misuse/abuse of prescription opioid analgesics, adolescents 12-17 years of age, United States: National Survey on Drug Use and Health, 2015-2017— Estimated number of individuals, in thousands (top panel) and percent of total adolescent population (bottom panel)



	Any	Hydro codone	Oxycodone	Codeine	Tramadol	Morphine	Fentanyl	Bupre norphine	Oxy morphone	Hydro morphone	Methadone	Other
2015	969	371	197		100	62	8	22	26	7	23	150
2016	881	349	254	318	64	46	8	18	28	5	22	163
2017	767	263	242	303	88	46	13	17	29	9	19	180



	Any	Hydro codone	Oxycodone	Codeine	Tramadol	Morphine	Fentanyl	Bupre norphine	Oxy morphone	Hydro morphone	Methadone	Other
2015	3.9%	1.5%	0.8%		0.4%	0.2%	0.0%	0.1%	0.1%	0.0%	0.1%	0.6%
2016	3.5%	1.4%	1.0%	1.3%	0.3%	0.2%	0.0%	0.1%	0.1%	0.0%	0.1%	0.7%
2017	3.1%	1.1%	1.0%	1.2%	0.4%	0.2%	0.1%	0.1%	0.1%	0.0%	0.1%	0.7%

NSDUH, National Survey of Drug Use and Health
*represent statistically significant changes relative to prior year
NOTE: Codeine was not included in the 2015 NSDUH survey

Source: SAMHSA detailed tables, Tables 1.98 A-B, 1.98D. Available from: https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.htm#tab1-98B. https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.pdf

Accessed on 7/18/2019. Note: NSDUH defines misuse of a drug as the following: "use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told."

Nearly 18% of adolescents who had used prescription opioids in the past year for any reason also reported past-year opioid misuse/abuse. The APIs with the highest prevalence of past-year misuse/abuse out of past-year any use were oxycodone, tramadol, and hydrocodone, with 27.8%, 24.1%, and 23.1% prevalence, respectively.

Table 4. National Survey on Drug Use and Health, 2017: Reported past year use or misuse/abuse of prescription pain relievers, by active ingredients, individuals aged 12 to 17

Active Pharmaceutical Ingredient	Past-Year Any Use (thousands)	Past-Year Misuse/Abuse (thousands)	Misuse/Abuse in Total Population (%)	Misuse/Abuse in Past-Year Any Users (%)
Any	4,346*	767	3.1	17.6
Hydrocodone	1,141	263	1.1	23.1
Oxycodone	869	242	1.0	27.8
Tramadol	364	88	0.4	24.1
Codeine	1,469	303	1.2	20.6
Morphine	374	46	0.2	12.3
Fentanyl***	59	13	0.1	**
Buprenorphine	61	17	0.1	**
Oxymorphone	73	29	0.1	**
Demerol®	31	2	0.0	**
Hydromorphone	32	9	0.0	**
Methadone	43	19	0.1	**
Other	2,016	180	0.7	8.9

*represent statistically significant changes relative to 2016
**figure not shown due to low precision
***estimate does not include illicit fentanyl

Source: SAMHSA detailed tables, Tables 1.98A-B Available from: https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.pdf Accessed on 7/9/2019. Note: NSDUH defines misuse of a drug as the following: "use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told"

As show in Table 6, the most common source from which adolescents obtained misused prescription opioids was a friend or relative (57%), most of which received their substance for free. The next most common source was a doctor (30%).

Table 6. Source Where Pain Relievers Were Obtained for Most Recent Misuse/Abuse U.S. Adolescents 12 to 17 years, 2016 and 2017: National Survey on Drug Use and Health

Source	Number, Thousands (2016)	Percent out of Adolescents Reporting Past-year Misuse/Abuse (2016)	Number, Thousands (2017)	Percent out of Adolescents Reporting Past-year Misuse/Abuse (2017)
Received through Prescription or Stolen from Provider	**205**	**26.3**	**199**	**31.6**
Prescription: One Doctor	165	21.2	177	28.1
Prescription: >1 Doctor	28	3.6	12	1.9
Stolen from Doctor's Office, Clinic, Hospital, or Pharmacy	12	1.5	10	1.6
Given by, bought from, or took from Friend/Relative	**449***	**57.4**	**360**	**57.0**
Given from Friend/Relative for Free	303	38.8	240	38.0
Bought from Friend/Relative	71	9.1	77	12.3
Taken from Friend/Relative without asking	74*	9.5	43	6.8
Bought from Drug Dealer/Stranger	**73***	**9.4**	**35**	**5.5**
Some Other Way**	**54**	**6.9**	**37**	**5.8**

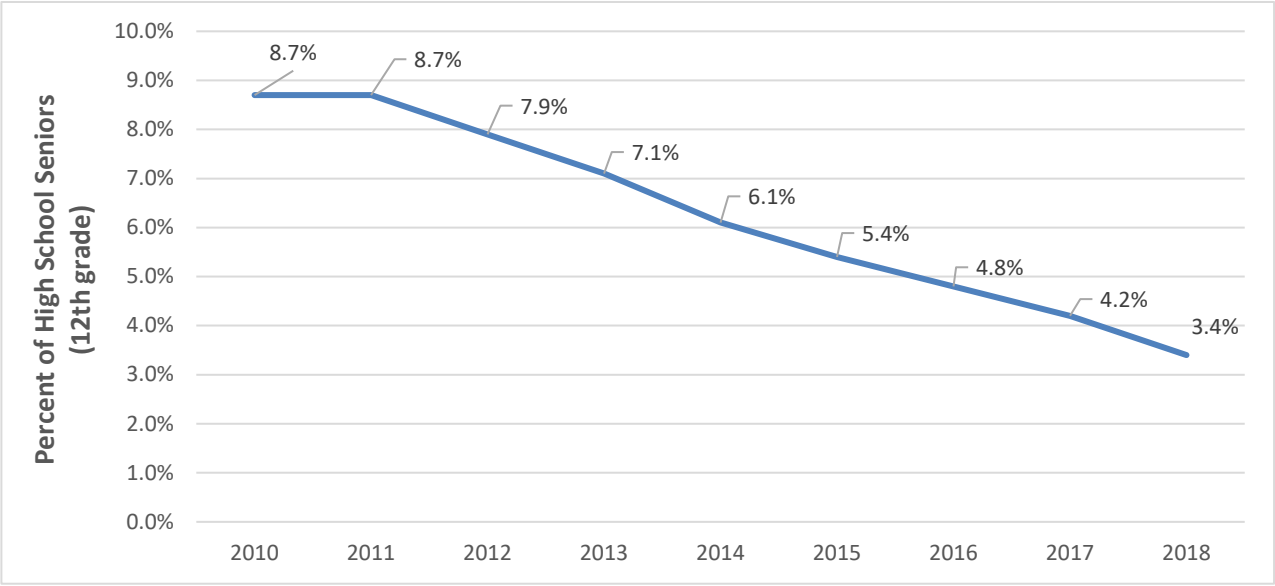
*represent statistically significant changes relative to 2016
**_Some Other Way_ includes write-in responses not already listed in this table or responses with insufficient information that could allow them to be placed in another category.

Source: SAMHSA detailed tables, Tables 6.53A-B Available from: https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.pdf Accessed on 7/18/2019.
NOTE: Respondents were asked to choose one of eight sources as their best answer. Respondents with unknown data on Source for Most Recent Misuse and respondents with unknown or invalid responses to the corresponding other-specify questions were excluded from the analysis.
Note: NSDUH defines misuse of a drug as the following: "use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told"

3.2 MONITORING THE FUTURE

As shown in Figure 2, in 2018, an estimated 3.4% of high school seniors reported past-year misuse/abuse of "narcotics other than heroin," (i.e., prescription opioids). The estimated prevalence of prescription opioid misuse/abuse among high school seniors declined significantly from 2017 to 2018, continuing a downward trend that began in 2011 (Figure 2).

Figure 2.
Past-year misuse/abuse of narcotics other than heroin, High School Seniors (12th grade), U.S., 2010-2018: The Monitoring the Future Study

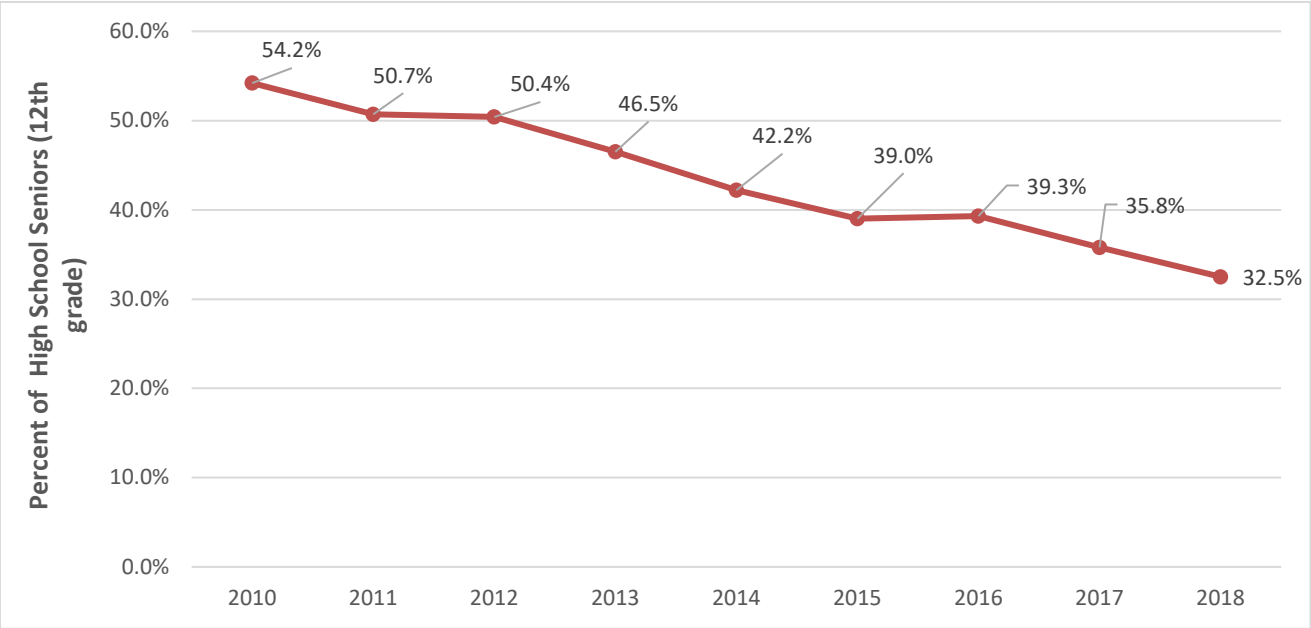


Source: The Monitoring the Future Study, the University of Michigan, Table 2.

Available from: Miech, R. A., Schulenberg, J. E., Johnston, L. D., Bachman, J. G., O'Malley, P. M., & Patrick, M. E. (December 17, 2018). "National Adolescent Drug Trends in 2018." Monitoring the Future: Ann Arbor, MI. Retrieved 7/22/2019 from http://www.monitoringthefuture.org/data/18data/18drtbl2.pdf

The reported ease of obtaining prescription opioids also declined over 2010-2018 (Figure 3). In 2018, 32.5% of 12th graders reported that these drugs were “fairly easy” or “very easy” to obtain, a decrease of 3.3% from 2017.

Figure 3.
Trends in Availability of Narcotics other than Heroin as Perceived by High School Seniors (12th grade), High School Seniors (12th grade), U.S., 2010-2018: The Monitoring the Future Study



Percent of 12th graders who answered the question "How difficult do you think it would be for you to get each of the following types of drugs, if you wanted some?" as "fairly easy" or "very easy" to get.

Source: The Monitoring the Future Study, the University of Michigan, Table 17.

Available from: Miech, R. A., Schulenberg, J. E., Johnston, L. D., Bachman, J. G., O'Malley, P. M., & Patrick, M. E. (December 17, 2018). "National Adolescent Drug Trends in 2018." Monitoring the Future: Ann Arbor, MI. Retrieved 7/22/2019 from http://www.monitoringthefuture.org/data/18data/18drtbl17.pdf

Nearly half (48.2%) of high school seniors who misused or abused prescription opioids within the past year obtained the substance for free from a friend or relative (Table 7). The most common method of obtaining misused prescription opioids was from a friend for free (40.2%) followed by one's own prescription (31.2%). Approximately 26% of high school seniors who misused prescription opioids reported purchasing the drugs from a friend, and 17.4% reported purchasing them from a drug dealer or a stranger (Table 7).

Table 7.
Source of Narcotics other than Heroin among those with past year misuse/abuse, High School Seniors (12th grade), U.S., 2010-2018: The Monitoring the Future Study

Source (Multiple Responses Allowed)	Percent of High School Seniors Who Reported Past-year Misuse/Abuse of (2017-2018)
Bought on Internet	3.6
Took from friend/relative without asking	**13.7**
Took from a friend without asking	0.5
Took from a relative without asking	13.7
Given for free by friend/relative	**48.2**
Given for free by a friend	40.2
Given for free by a relative	16.4
Bought from friend/relative	**26.1**
Bought from a friend	26.1
Bought from a relative	3.3
From a prescription I had	**31.9**
Bought from drug dealer/stranger	**17.4**
Other method	14.5

Percent of 12th graders who answered the question "Where did you get the [prescription narcotic] you used without a doctor's orders during the past year? (Mark all that apply)"

NOTE: Responses not mutually exclusive.

MTF, Monitoring the Future
Source: The Monitoring the Future Study, the University of Michigan, Table 9-10.

Available from: Miech, R. A., Johnston, L. D., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., & Patrick, M. E. (2018). Monitoring the Future national survey results on drug use, 1975-2017: Volume I, Secondary school students. Ann Arbor: Institute for Social Research, The University of Michigan.
Available at http://www.monitoringthefuture.org/pubs/monographs/mtf-vol1_2018.pdf

3.3 NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM- COOPERATIVE ADVERSE DRUG EVENT SURVEILLANCE (NEISS-CADES) ANALYSIS

In 2016 and 2017, there were an estimated 267,020 ED visits per year for adverse events attributed to use of a prescription opioid product. An estimated 10,875 (4.1%) of these visits occurred in patients under 18 years, and over half (57.6%) of pediatric visits involved adolescents between 12 and 17 years. Based on annual national estimates, 41.7% of prescription opioid-related ED visits in adolescents were due to self-harm, and 34.0% were due to nonmedical use (i.e., abuse, therapeutic misuse, or overdose without indication of intent).

As shown in Table 8, among adolescents, the population rate of ED visits related to nonmedical use of prescription opioids was 8.5 per 100,000, which was substantially lower than the rate in adults (49.9 per 100,000). The rate of ED visits for patients ages 0-11 was 9.5 per 100,000 for therapeutic prescription opioid use, 82.5% of which were unsupervised medication ingestions, and negligible for other intents. The rate of ED visits due to prescription opioid self-harm was not significantly different between adolescents and adults (respective estimates 10.5 and 13.3 per 100,000).

Table 8. National Estimates of ED Visits for Adverse Events from Use of Prescription Opioid Containing Products, by Intent of Drug Use, 2016-2017				
Age Group	Cases*	Average Annual Estimate	Annual Rate per 100,000**	95% CI of Rate
Nonmedical Prescription Opioid Use+ (Total Annual Estimate = 127,177 ED Visits)				
Ages 0-11	0	***		
Ages 12-17	89	2,130	8.5	4.4-12.6
Ages 18 and older	3,714	124,980	49.9	36.2-63.6
Therapeutic Prescription Opioid Use‡ (Total Annual Estimate = 103,786 ED Visits)				
Ages 0-11¥	212	4,600	9.5	6.3-12.6
Ages 12-17	53	1,522	6.1	4.0-8.2
Ages 18 and older	2,655	97,664	39.0	28.0-50.0
Prescription Opioid Self-harm (Total Annual Estimate = 36,057 ED Visits)				
Ages 0-11	2	***		
Ages 12-17	132	2,617	10.5	6.0-14.9
Ages 18 and older	908	33,374	13.3	10.5-16.1
*Data are from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project, CDC. Age missing for 3 cases of nonmedical use and 1 case of self-harm. **Rates are based on average Census population estimates for each age group for 2016 and 2017. ***Estimates based on <20 cases or total estimates <1,200 are considered statistically unstable and are not shown (***).				
+Includes abuse of a medication, therapeutic misuse (use other than as directed by a clinician), and opioid overdoses without indication of intent.				
‡Includes adverse events from therapeutic use (e.g., adverse effects, allergic reactions, medication errors, and unsupervised ingestions by children).				
¥82.5% of these ED visits were due to unsupervised ingestions				
Source: Data provided by the CDC Division of Healthcare Quality Promotion				
Notes: Population estimates are based on the 2010 Census and reflect changes to the April 1, 2010 population due to the Count Question Resolution program and geographic program revisions. For population estimates methodology statements, see http://www.census.gov/programs-surveys/popest/technical-documentation/methodology.html. Opioids related to Medication Assisted Treatment, such as buprenorphine-naloxone, were included in the ED visit estimates.				

3.4 POISON CONTROL CENTER CALLS INVOLVING PRESCRIPTION OPIOID EXPOSURES IN CHILDREN AND ADOLESCENTS IN THE UNITED STATES: 2000-2015

Allen et al. (5) analyzed data from records of calls to PCCs involving pediatric prescription opioid exposures (single-substance only), 2000 to 2015. Key findings of this study are shown in Table 9. From 2000-2015, the overall rate of calls to poison control centers for single-substance opioid exposures was 14.3 per 100,000 children (<20 years old). Most of these reported exposures occurred in children between the ages of 0 to 5 (59.7%) followed by teenagers aged between 13 and 19 years (29.9%). The most

commonly identified opioid APIs in all age groups were hydrocodone, oxycodone, and codeine, and the most common formulation was oral solid.

In children aged five years or less, 85.5% of opioid exposure calls were classified as "Unintentional-General" and 13.4% classified as "Unintentional Therapeutic Error" The most common reason for opioid exposure in children ages 6 to 12 years was "Unintentional Therapeutic Error". In contrast, 71.5% of opioid exposure calls involving teenagers were for intentional exposures: 34.2% were suspected suicides, 20.8% abuse, 11.2% misuse, and 5.3% intentional-unknown.
Teenagers were more likely to be admitted to a health care facility following opioid exposure and were the least likely to receive no health care treatment compared to children in other age groups. Teenagers were more likely to have an opioid exposure that resulted in a Major or Moderate effect†† and were least likely to have an exposure resulting in "No Effect" compared to children in other age groups. Sixty-eight children ages 0 to 5, eleven children ages 6 to 12, and ninety-six teenagers died following prescription opioid exposure.

Table 9. Characteristics of Prescription Opioid Single-substance Exposures Among Children <20 Years by Age Group, NPDS 2000-2015

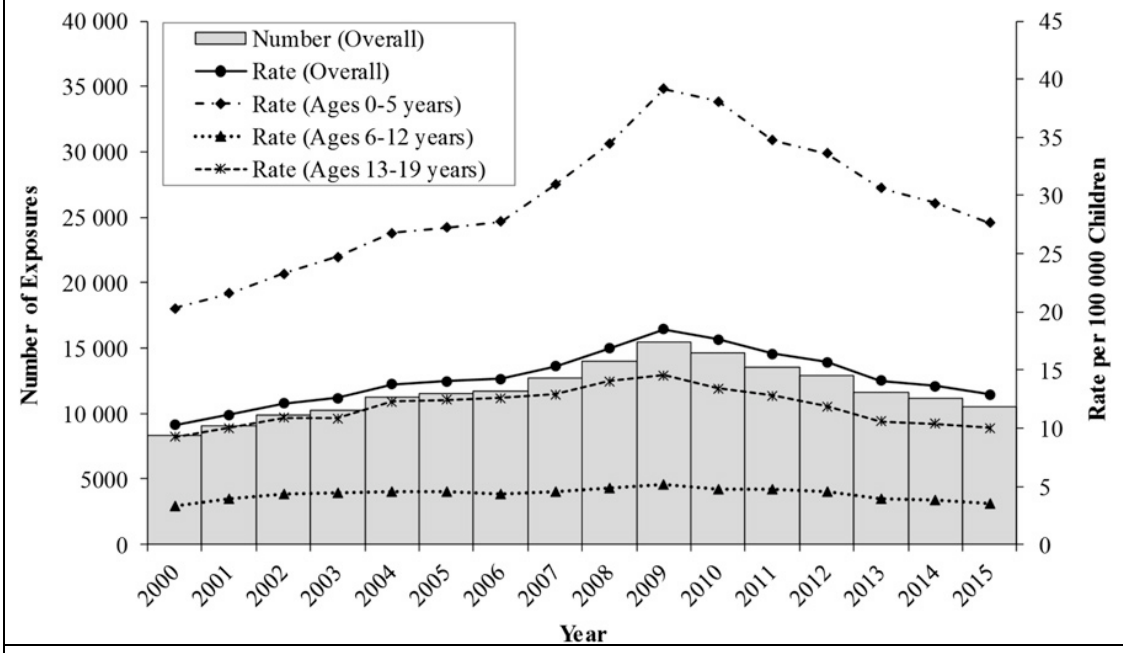
	Age Group, *n* (%)		
Characteristics	**Ages 0-5 years**	**Ages 6-12 years**	**Ages 13-19 years**
Overall ***(****Row percent)***	112,465 (59.7)	19,723 (10.5)	56,280 (29.9)
Reason†			
Unintentional-general	96,134 (85.5)	5,905 (29.9)	3,759 (6.7)
Unintentional-therapeutic error	15,124 (13.4)	10,749 (54.5)	8,292 (14.7)
Intentional- overall	201 (0.1)	1,988 (10.1)	40,255 (71.5)
Intentional- suspected suicide	**46 (0.0)**	**360 (1.8)**	**19,239 (34.2)**
Intentional-abuse	**40 (0.0)**	**447 (2.3)**	**11,721 (20.8)**
Intentional-misuse	**86 (0.1)**	**670 (3.4)**	**6,297 (11.2)**
Intentional-unknown	29 (0.0)	511 (2.6)	2,998 (5.3)
Other	643 (0.6)	560 (2.8)	2,663 (4.7)
Unknown	363 (0.3)	521 (2.6)	1,341 (2.4)
Type of Opioid			
Hydrocodone	29,088 (25.9)	5,447 (27.6)	19,491 (34.6)
Oxycodone	20,011 (17.8)	3,205 (16.3)	9,968 (17.7)
Codeine	19,151 (17.0)	5,025 (25.5)	6,938 (12.3)
Tramadol	12,403 (11.0)	1,778 (9.0)	7,115 (12.6)
Propoxyphene	5,799 (5.2)	748 (3.8)	3,363 (6.0)
Morphine	3,781 (3.4)	576 (2.9)	1,928 (3.4)
Methadone	3,466 (3.1)	533 (2.7)	2,218 (3.9)
Buprenorphine	5,078 (4.5)	174 (0.9)	509 (0.9)
Meperidine	422 (0.4)	147 (0.7)	236 (0.4)
Hydromorphone	330 (0.3)	75 (0.4)	129 (0.2)
Fentanyl	222 (0.2)	28 (0.1)	163 (0.3)
Oxymorphone	183 (0.2)	22 (0.1)	132 (0.2)
Other	12,531 (11.1)	1,965 (10.0)	4,090 (7.3)

†† "Major Effect" is defined as exhibiting life-threatening or disabling symptoms as a result of exposure. "Moderate Effect" is defined as experiencing non-life-threatening symptoms that result in likely needing treatment as a result of exposure. Further detail is provided in Section 7.2 of this review.

Table 9 Continued. Characteristics of Prescription Opioid Single-substance Exposures Among Children <20 Years by Age Group, NPDS 2000-2015			
	Age Group, *n* (%)		
Characteristics	**Ages 0-5 years**	**Ages 6-12 years**	**Ages 13-19 years**
Formulation			
Solid	78,495 (69.8)	11,204 (56.8)	45,797 (81.4)
Liquid	20,623 (18.3)	6,052 (30.7)	3,215 (5.7)
Other	2,297 (2.0)	245 (1.2)	1,122 (2.0)
Unknown	11,050 (9.8)	2,222 (11.3)	6,146 (10.9)
Level of Care Received			
Admitted to HCF	9,824 (8.7)	794 (4.0)	12,091 (21.5)
Treated/evaluated and released	35,736 (31.8)	2,810 (14.2)	13,992 (24.9)
Lost to follow-up/left AMA	7,898 (7.0)	1,672 (8.5)	8,224 (14.6)
Refused referral/did not arrive at HCF	5,746 (5.1)	1,241 (6.3)	4,751 (8.4)
No HCF treatment received	53,261 (47.4)	13,206 (67.0)	17,222 (30.6)
Medical outcome‡			
Death	68 (0.1)	11 (0.1)	96 (0.2)
Major Effect	772 (0.7)	63 (0.3)	1,145 (2.0)
Moderate Effect	4,092 (3.6)	506 (2.6)	5,628 (10.0)
Minor Effect	13,957 (12.4)	2,917 (14.8)	14,712 (26.1)
No Effect	52,145 (46.4)	5,020 (25.5)	9,649 (17.1)
Not Followed/Unable to Follow	41,431 (36.8)	11,206 (56.8)	25,050 (44.5)
†Further detail on Reason provided in Appendix A. ‡Further detail on Medical Outcome provided in Appendix B.			
NPDS, National Poison Data System As reported in Tables 1 and 2 of publication: Allen JD, Casavant MJ, Spiller HA, et al. Prescription Opioid Exposures Among Children and Adolescents in the United States: 2000-2015. *Pediatrics*. 2017; 139 (4): e20163382. DOI: 10.1542/peds.2016-3382			

As shown in Figure 4, poison control center calls involving single-substance, prescription opioid exposures in children and adolescents increased significantly from 2000 to 2009, in both number and rate per 100,000 population, followed by a significant decline from 2009 to 2015. The age-group specific rates of opioid exposures all showed a similar pattern of increase followed by decline. Over all years, the rate of opioid exposures was highest among children between 0 and 5 years and lowest among children between ages 6 and 12 (Figure 4). These trends were not consistent across all reasons for exposure, however, as the rate of prescription opioid-involved suspected suicide among teenagers increased by 52.7% from 2000 through 2015(5).

Figure 4. Annual Number and Rate of Prescription Opioid Exposures among Children by Age Group, NPDS 2000-2015



NPDS, National Poison Data System

As reported in Figure 2 of publication: Allen JD, Casavant MJ, Spiller HA, et al. Prescription Opioid Exposures Among Children and Adolescents in the United States: 2000-2015. *Pediatrics*. 2017; 139 (4): e20163382.

DOI: 10.1542/peds.2016-3382

3.5 Review of the Epidemiologic Literature On Risk of adverse outcomes Following Prescription Opioid Therapy in Pediatric Populations

The results of our literature review are summarized in tabular form in Appendix E.

3.5.1 Association between medical use of prescription opioids and future risk of opioid analgesic misuse, abuse, or substance use disorder

Eight out of ten studies identified in our search examined the association between medical use of prescription opioids in pediatric populations and prescription opioid misuse/abuse or SUD (6-12,31). Two were cross-sectional studies (6,8) and six were longitudinal cohort studies (7,9-12,31), all of which included only adolescents. In addition, we reviewed two studies that examined other adverse outcomes, such as non-fatal overdose or opioid-related ED visit or hospitalization, following prescription opioid exposure (13,14).

One longitudinal cohort study used questionnaire data to assess the association between medical use of prescription opioid analgesics and subsequent misuse/abuse of opioid analgesics among students in 7th through 11th grade at baseline (year 1) (7). Students

responded to the Secondary Student Life Survey (SSLS), a survey that was modeled after the MTF. **Compared to students who reported no opioid analgesic exposure at baseline, students who reported baseline medical use only were more likely to report misuse/abuse at one-year follow-up, in an unadjusted analysis** of the following outcomes: misused or abused opioid analgesics from their own prescription (7.6% *vs.* 2.0%), misused someone else's opioid analgesics for pain relief (4.0% vs. 1.7%), and misused or abused someone else's opioid analgesics for other reasons (2.9% vs. 1.3%). Analysis of cross-sectional data from middle and high school students found the peak risk of opioid analgesic misuse/abuse was observed at age 16: 2% (6). Medical use of opioid analgesics by age 12 was associated with a doubling in the rate of misuse/abuse, compared with medical use after 12 (adjusted HR=2.02; CI:1.08-3.75) (6).

In another set of studies, MTF assembled longitudinal cohorts, consisting of individuals who completed the survey as high school seniors, to examine the association between medical and nonmedical use of prescription opioids in the 12th grade and future risks of misuse/abuse and SUD symptoms. One of these longitudinal cohort studies followed up students three times from ages 19 to 23 to assess for self-reported misuse/abuse (9). **In this study, past-year medical use of prescription opioids at age 18 was associated with a 33% higher risk of misuse/abuse at ages 19-23**, adjusted for past marijuana use and disapproval of use, cigarette smoking, prescription opioid and/or sedative misuse, binge drinking, sex, school grades, race/ethnicity, and having a parent with a college degree (RR=1.33; CI:1.04-1.70). When this analysis was stratified based on other risk factors associated with future risk of abuse, such as history of other substance use or approval of marijuana use, medical use of prescription opioids was associated with a significantly higher risk of misuse/abuse only among students who did not have these other risk factors for future misuse/abuse. Medical use of prescription opioids was associated with a higher risk of future misuse/abuse most strongly among students who did not use other drugs previously.

Other MTF longitudinal cohort studies followed up individuals who graduated in 1976-1996 to examine the associations between medical use of prescription opioids in high school seniors and risks of misuse/abuse and symptoms of SUD in the past five years at age 35 (10,11). (The earlier study [10] analyzed the association with SUD symptoms among a subset of the sample in the later study [11] and produced similar results.) **Individuals who indicated lifetime medical use of opioid analgesics at age 18 had higher odds of past year misuse/abuse at age 35, compared to those who had no history of opioid exposure at age 18** (AOR=1.74; CI: 1.10-2.76), adjusted for demographic characteristics, year of baseline survey, and baseline use of alcohol and other drugs besides opioids. **Opioid analgesic medical use only (i.e., without misuse/abuse) in adolescence was <u>not</u> associated with self-reported symptoms of SUD at age 35 (11).** However, misuse/abuse of opioid analgesics in adolescence <u>was</u> associated with symptoms of SUD at age 35 (11). Also, compared to respondents reporting no opioid exposure at age 18, those who reported misuse/abuse without medical use, or both medical use and misuse/abuse, at age 18 were at a higher risk of future misuse/abuse at age 35 (respective AORs were: 2.09; CI: 1.10-3.96; and AOR=3.22; CI: 1.93-5.36) (11).

The most common type of prescription opioid exposure in high school seniors consisted of only medical use of prescription opioids (8), and **for students with a history of both medical and nonmedical use of prescription opioids, medical use most often preceded the initiation of nonmedical use** (8). A multi-year cross-sectional analysis of MTF survey data (8) observed that trends in medical and nonmedical use of opioid analgesics were parallel from 1976 to 2015.

Finally, a retrospective cohort study used a large, commercial health insurance claims database to investigate the association between an opioid analgesic prescription from a dentist and the risk of "opioid abuse" in the 12 months post-prescription among adolescents (ages 16-18) and young adults (ages 19-25) who had no opioid analgesic prescription in the previous 12 months (12). Here, the outcome, opioid abuse, was defined as at least one ICD-9 or ICD-10 healthcare claim diagnosis code for opioid abuse, opioid use disorder, or opioid overdose. **Filling an opioid analgesic prescription from a dentist was associated with a 5.3% (CI: 5.0%-5.7%) absolute increase in risk of having a subsequent healthcare claim for opioid abuse,** adjusted for patient race/ethnicity and history of non-opioid substance use. Exposed patients had a significantly higher risk of a healthcare encounter with an opioid abuse-related claim, regardless of the setting – office visit, ED, or hospitalization (5.8% among exposed patients vs. 0.4% among unexposed patients). There was one death each in the opioid-exposed (n=14,888) and non-exposed (n=29,776) groups; cause of death was not described.

3.5.2 Descriptive studies of prescription opioids and opioid-related adverse outcomes

Bell et al. (31) estimated the occurrence of either opioid overdose or SUD diagnosis, as determined by healthcare claims data, over five years following adolescent admission to a trauma center for serious injury. Nearly all patients (97%) were prescribed opioids upon discharge, so the investigators did not compare risks relative to an unexposed reference group. Also, approximately 15% and 5% of patients screened positive for alcohol and drugs at the time of admission, respectively, and these were independent risk factors for both outcomes. **Within five years of admission, 8% of adolescent trauma patients experienced an opioid overdose, and 14% had a SUD diagnosis based on claims data.** The authors note that, because this study population may have been at higher risk of SUD before their opioid analgesic treatment, it is difficult to determine whether the exposure to medical prescription opioids led to the development of SUD or whether other factors were responsible for the high percent of subsequent SUD claims.

A retrospective cohort study identified opioid-related adverse events during and immediately following the days' supply of an outpatient opioid analgesic prescription by reviewing medical records from ED visits, hospital admissions, or deaths (autopsy report), in Tennessee Medicaid recipients, age 2 to 17 years, from 1999 to 2014 (13). **In this 16-year period, the study identified 36 cases of ED visits, hospitalizations, or deaths due to prescription opioid abuse among 12 to 17-year-olds with a current opioid analgesic prescription, a population that consisted of an average 26,156 adolescents each year.**

Chatterjee et al. (14) examined the percent of individuals who had a documented prescription in the previous 12 months prior to non-fatal opioid overdose. This study captured information for adults (ages 18 and older) and adolescents (ages 12 to 17) who experienced non-fatal opioid overdose based on ICD-9 code in the Massachusetts All Payer Claims Database, 2012 to 2014. Only 1% of the total sample consisted of adolescents (n=195) between the ages of 11 and 17, most of whom were between 15 and 17 years of age. Approximately 11% of the adolescents who were identified as having experienced a non-fatal overdose in the analysis period had a documented prescription for an opioid analgesic in the previous 12 months. However, adults who experienced non-fatal opioid overdose were far more likely to have had a prescription for opioid analgesics within the past 12 months (43%).

3.5.3 Association between misuse/abuse of prescription opioids and heroin initiation in adolescents

To supplement the main literature review, we also briefly examined the association between opioid analgesic misuse/abuse in adolescent populations and the risk of transitioning to heroin use. In this section, we briefly summarize the findings of two recent, key studies that explore this potential sequela of adolescent opioid analgesic misuse/abuse.

Kelley-Quon et al. (33) examined the association between opioid analgesic misuse/abuse in adolescence and heroin initiation using a longitudinal cohort of high school students with no previous heroin use at baseline (9^{th} grade). Students were assessed every 6 months from 9^{th} to 12^{th} grade, in-class, via telephone, internet, or mail. Participants reported past 30-day and/or 6-month opioid analgesic misuse/abuse and past 6-month or lifetime heroin use at each semiannual follow-up. Students who reported current or prior opioid analgesic misuse/abuse were at a significantly higher risk of heroin initiation by the end of high school (Current HR 3.18: 95 CI 1.68-6.02; Prior HR 2.09: 95 CI 1.14-3.83), compared to students reporting no opioid analgesic misuse/abuse. Current opioid analgesic misuse/abuse was more strongly associated with subsequent heroin use than was current use of other substances, including cannabis, alcohol, cigarettes, or other nonopioid drugs. Opioid analgesic misuse/abuse was also positively associated with heroin initiation among adolescents in a cross-sectional analysis of NSDUH survey data (32). Respondents who reported initiating opioid analgesic misuse/abuse between ages of 10 and 12 had the highest prevalence of heroin use in adolescence (32).

4 DISCUSSION

4.1 NATIONAL ESTIMATES OF OPIOID ABUSE, MISUSE, AND RELATED OUTCOMES

4.1.1 Summary

The U.S. prevalence of past-year, prescription opioid misuse/abuse in 2017 was 3.1% among adolescents age 12-17 and 4.2% among high school seniors, according to estimates from national surveys, NSDUH and MTF. Both surveys have observed a downward trend in prescription opioid misuse/abuse among adolescents in recent years.

Over this same time period, the percent of high school seniors reporting that prescription opioids were easy to obtain also declined, from 50.7% in 2011 to 32.5% in 2018. The most common source of prescription opioids for misuse/abuse was from a friend or relative (57%), while approximately 30% obtained them from their own prescription. Based on both national surveys and poison control center calls, the most commonly misused/abused opioids among adolescents were hydrocodone, oxycodone, tramadol, and codeine. The preponderance of these four APIs among self-reports of prescription opioid misuse/abuse and poison center exposure calls is consistent with FDA's review of opioid analgesic utilization, in this background package, which found that the five most frequently prescribed opioid analgesics in the pediatric population (0-17 years) were hydrocodone-acetaminophen, codeine-acetaminophen, oxycodone-acetaminophen, single-ingredient oxycodone and tramadol products (Figure 1 of the Drug Utilization Review of U.S. Outpatient Utilization Patterns of Opioid Analgesics, in this background package).

Overall, ED visits for adverse events due to prescription opioid use are more common among adults and adolescents than younger children. Approximately 4.1% of ED visits for prescription opioid adverse events occurred in patients under the age of 18, more than half of which occurred in patients between 12 and 17 years old. In 2016-2017, there were an estimated 2,130 ED visits annually attributed to nonmedical use of prescription opioids by adolescents. Among adolescents, the population rate of ED visits due to nonmedical use of prescription opioids (8.5 per 100,000) was lower than the rate in adults (49.9 per 100,000). However, the rate of ED visits for self-harm involving prescription opioids was only slightly higher for adult patients (13.3 per 100,000) than for adolescent patients (10.5 per 100,000).

From 2000-2015, U.S. poison control centers received 18,018 exposure calls involving single-substance misuse or abuse of prescription opioids among teenagers. Thirty-four percent of these calls were due to suspected suicide and 32% were due to misuse or abuse. The rate of all prescription opioid exposure calls among teenagers showed minimal net change from 2000-2015; however, the rate of calls for suspected suicide increased by 52.7%. Whereas most prescription opioid-related calls involved unintentional exposures in children ages 5 years or less, teenagers were more likely to have an intentional exposure, to be admitted to a health care facility, and to have a more serious medical outcome.

Notably, self-harm was a frequent reason why adolescents were presenting for medical assistance for harms from exposure to prescription opioids, with respect to both ED visits and poison control center calls (5).

4.1.2 Limitations of Data

National Survey Data: NSDUH and MTF

Although NSDUH and MTF are capable of producing national estimates of drug misuse and abuse, they are subject to the inherent limitations of self-reported data, such as non-response bias, misclassification, and recall bias. Additionally, individuals with advanced substance use disorders may be underrepresented, particularly if they become homeless, incarcerated, enter a residential treatment facility, or, for MTF, if they are absent from

school or have dropped out. In NSDUH, individuals under the age of 12 are not surveyed, therefore we are not able to determine the prevalence of prescription opioid misuse in children under 12 years of age. MTF only reports prescription opioid misuse among sampled high school seniors, due to potential inaccuracy of report from 8th and 10th graders, therefore reported results from MTF only reflect prescription opioid misuse rates and behaviors among adolescents in the 12th grade.

ED Visits Data: NEISS-CADES

NEISS-CADES data can be used to calculate national estimates of ED visits for adverse events attributed to medication use, but NEISS-CADES does not include cases that do not result in an ED visit or that result in death before or during ED evaluation. NEISS-CADES also does not include cases of people presenting to the ED due to inadequate therapy or drug withdrawal. The quality of these surveillance data depends on the completeness and accuracy of medical record documentation by the healthcare provider and, to be included in NEISS-CADES, cases require documentation by the healthcare provider that a drug or drug class (e.g., "prescription opioid") was implicated in the ED visit.

Poison Control Center Call Data: NPDS

PCC call data should not be interpreted as representing the complete incidence of national exposures or cases of misuse/abuse related to any substance. Of note, calls for exposure to multiple substances were excluded from this analysis, and this likely under-estimates misuse/abuse of prescription opioids. PCC data rely on information shared by patients and healthcare personnel, and most substance classification does not involve any biologic confirmation. Drug exposures resulting in unattended or out-of-hospital death are unlikely to generate a call to a PCC, and therefore, fatal poisonings are expected to be substantially under-reported in PCC call data. Follow-up and medical outcomes were not available for a substantial minority of calls. It is possible that changes in PCC rates in part reflect changes in public and professional awareness of the risks associated with specific drugs, and awareness of the abuse potential of a drug among call center personnel could also increase the likelihood of an exposure being coded as intentional abuse. Call rates may also be influenced by general changes in use of PCCs over time.

4.2 Review of the Epidemiologic Literature On Risk of adverse outcomes Following Prescription Opioid Therapy in Pediatric Populations

4.2.1 Summary

We found evidence from longitudinal survey studies (7,9,10) and a retrospective claims-based study (12) suggesting that medical use of prescription opioids is modestly associated with a future risk of prescription opioid misuse/abuse in later adolescence and adulthood, even after controlling for measurable confounding factors. In contrast, medical use of prescription opioids in adolescence was not found to be associated with SUD symptoms at age 35 (11). There are scarce data on the risks of SUD and other serious outcomes, such as overdose, following medical use of opioid analgesics (11-13,31) in children and adolescents. Healthcare claims with ICD codes indicating SUD were found in 14% of adolescent patients within five years following discharge from

trauma center for serious injury (the vast majority of whom are prescribed opioids). This finding is likely, at least in part, related to the trauma population being enriched with individuals at higher risk for SUD. In a study of non-fatal opioid overdose in Massachusetts, 2012-2014, only about 11% of the adolescent patients had a documented prescription for an opioid analgesic in the prior 12 months. This is not surprising given the evidence from national surveys that adolescents' most common sources of prescription opioids for misuse or abuse are friends and relatives. Limited literature suggests that opioid analgesic misuse/abuse in adolescence is a risk factor for future heroin use (32,33) and for later opioid analgesic misuse/abuse and SUD symptoms (11). More longitudinal studies are needed investigating relationships between opioid analgesic therapy, misuse/abuse of prescription opioids, use of heroin and other illicit opioids, and the development of SUD across various adolescent populations.

4.2.2 Limitations of the data

We must consider the evidence of these published studies in light of the strengths and limitations of different study designs. Key limitations are discussed here, and additional reviewer comments on individual studies can be found in Appendix E.

Longitudinal cohort studies provided the strongest assessment of the risks associated with prescription opioid exposures. However, the results of these studies varied largely on how medical opioid use and outcomes were defined. The study of the association between an opioid analgesic prescription from a dentist and subsequent misuse/abuse defined prescription opioid exposure based on previous claims (12), whereas the other reviewed studies (6,7,8,9,10) relied on student response of past medical opioid use. Opioid analgesic misuse/abuse was defined similarly across all studies, which may explain the consistency of the association observed by multiple studies. Substance Use Disorder, however, was defined differently across studies and was also assessed at different time points following medical use of prescription opioids. McCabe's (10,11) studies defined SUD based on two or more symptoms consistent with the DSM-IV or V, yet Bell (31) defined SUD based on an abuse diagnosis code associated with a healthcare encounter. Studies that relied on longitudinal surveys were able to measure both outcome and exposure based on patient report. However, the accuracy of prescription opioid medical and nonmedical use may be affected by the period of recall (e.g., lifetime, past year, or past 30 days). Additionally, the presence of SUD symptoms does not necessarily imply that an individual would receive a SUD diagnosis from a physician. An additional consideration in McCabe's studies (10,11) examining misuse and abuse at age 35 is the potential for bias due to loss to follow-up. It is possible that some individuals who had developed SUD were unable to be included in the follow up sample due to incarceration, substance abuse treatment or rehabilitation admission, institutionalization, or death. However, we do not believe this affected the observed study results as the number of individuals lost to follow up was not different between adolescent medical and nonmedical opioid users.

Another limitation of these studies is that the observed results could be affected by unmeasured confounding, as studies were likely not able to accurately measure all variables that could be associated with both prescription opioid exposure and outcome(s) such as opioid misuse/abuse, SUD, and overdose. These might include such factors as

unreported personal or family history of substance use, physical or emotional abuse in childhood, unmeasured chronic pain (29), injury (30), or other factors associated with a higher risk of future opioid analgesic misuse/abuse and SUDs.

Claims-based studies have several unique limitations when examining the association between prescription opioid exposure and the risk of future substance abuse and related adverse outcomes. First, we cannot infer that all patients consumed opioids after filling a prescription for opioid analgesics, and claims data will not reflect prescriptions for which cash was paid. The ascertainment of outcome also relies on administrative claims, and therefore, an adverse event for which medical care was not sought and billed for would not be captured. Claims-based outcomes used in these studies were not independently validated nor verified and therefore may not accurately reflect diagnoses. Finally, the accuracy of claims-based outcomes also depends on healthcare providers' identifying and documenting SUDs. Similar to the longitudinal survey-based studies, there are likely to be unmeasured confounders in claims-based studies.

The cross-sectional studies we reviewed relied on patient report of past medical opioid use (6,8). These results could be biased due to differential recall of past medical exposure to prescription opioids based on current opioid analgesic misuse/abuse at the time of survey. The reviewed case series (14,31) identified some important patient risk factors, such as positive drug or alcohol screen at the time of trauma, that may be associated with elevated risk of overdose or SUD outcome in adolescent patients exposed to prescription opioids (31). They also help us to understand the role of prescribed vs non-prescribed opioids in adolescent overdoses. (14). While these studies presented interesting results that warrant further investigation, we were not able to draw conclusive inferences regarding the risks of prescription opioid exposures from these results.

In general, the literature reviewed lacked information on the quantity of prescription opioids consumed, the reason for medical use (i.e. what condition/procedure opioids were prescribed for), and the length of time the individual used opioids for medical purposes. Information on more specific patterns of medical use of opioids may have provided additional insight into understanding the nuances of the relationship between medical use of prescription opioids in children and adolescents and the future risk of misuse and abuse related outcomes.

5 CONCLUSION

National survey data indicate that adolescent prescription opioid misuse and abuse have been declining in recent years, with the most recent data estimating that approximately 3-4% of adolescents have misused or abused prescription opioids in the past year. Among adolescents who misuse or abuse prescription opioids, most received them from a friend or relative, although nearly a third obtained them via their own prescription. Adolescents perceive prescription opioids as becoming more difficult to obtain for misuse and abuse. The rate of ED visits due to nonmedical use of prescription opioids is lower among adolescents than among adults. Among adolescents, ED visits due to self-harm involving prescription opioids occur at slightly higher rates than visits due to nonmedical

prescription opioid use. Most opioid-related poison control center exposure calls involved children ages 5 years and younger; however, prescription opioid exposure calls in adolescents were more likely to involve misuse/abuse or suicide attempts and to result in serious adverse outcomes.
From 2000-2015, calls involving intentional prescription opioid exposures in adolescents increased from 2000-2009 and then declined from 2009-2015, whereas calls involving adolescent suicide attempts, specifically, increased 52% over the entire study period.

Limited evidence suggests that medical use of opioid analgesics may place adolescents at modestly increased risk of future misuse or abuse. Longitudinal data suggest that opioid misuse and abuse during adolescence are associated with substance use disorders (SUDs) in adulthood; however, medical opioid use alone in adolescence does not appear to increase the risk of SUD in adulthood. Misuse and abuse of prescription opioids in adolescence also carries an increased risk of subsequent heroin use. More research is needed examining the relationships between legitimate medical use, misuse, and abuse of prescription opioids, substance use disorders, and related adverse outcomes, while fully accounting for potential confounding factors such as ongoing pain, use of other substances, and psychosocial factors.

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7 APPENDICES

7.1 APPENDIX A: NPDS DEFINITIONS OF EXPOSURE REASONS

NPDS Definitions for Intentional Exposure Reason Categories from the NPDS Data Dictionary		
Intentional Exposure Reasons	**NPDS Definition**	**Case Inclusions/ Exclusions examples**
Suspected Suicides	"An exposure resulting in the inappropriate use of a substance for self-harm or self-destruction or manipulative reasons."	"Case Inclusions: Suicides, suicide attempts, and suicide gestures, whether suspected or confirmed • Cases in which history indicates patient was upset or depressed • Patients who provide explanations for their actions such as "arguing with parents," "disturbed about poor grades," or "having marital problems" • Ingestions of large quantities of one or more drugs where the only likely explanation is the patient's intent to harm himself"
Abuse	"An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect", including recreational use of a substance for any effect.	"Case Inclusions: A person who inhales helium to talk funny • A person who uses GHB at a dance club • An infant with toxic effects or withdrawal symptoms as a result of the mother's drug abuse while the child was in utero or while breast-feeding"
Misuse	"An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect."	**Case Inclusions:** A person deliberately mixes or applies a pesticide inappropriately, so it will be more effective • A person deliberately increases the dosage of a medication to enhance its therapeutic effect • Overuse of caffeine to study for an exam **Case Exclusions:** Patients who want to get high (should be INTENTIONAL ABUSE) • Suspected child abuse (should be OTHER-MALICIOUS)"
Unknown	Exposures that are deemed to be intentional although the specific motive is undetermined.	N/A

7.2 APPENDIX B: NPDS DEFINITION FOR MEDICAL OUTCOME

NPDS Definitions for Medical Outcome from the NPDS Data Dictionary	
Medical Outcome	**NPDS Definition**
No Effect	"The patient developed no symptoms (clinical effects) as a result of the exposure. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that the poison center is reasonably certain no effects will occur."
Minor Effect	"The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and often involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of well-being and has no residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not worsen. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance."
Moderate Effect	"The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening and the patient has returned to a pre-exposure state of well-being with no residual disability or disfigurement. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance."
Major Effect	"The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the symptoms are anticipated to be long-term or permanent**."**

7.3 APPENDIX C: NEISS-CADES DEFINITIONS OF DRUG-RELATED ADVERSE EVENTS

NEISS-CADES Definitions of Case Type		
Analytic Category		**NEISS-CADES Definition**
Nonmedical Use	ABUSE	Clinician diagnosis of abuse (for current ED visit) or documentation of recreational use (e.g., "to get high", "at a party", "crushing and snorting", "bought off street")
	THERAPEUTIC MISUSE	Documentation of therapeutic intent, but use was not as directed (e.g., taking someone else's prescription medication for pain, intentionally taking larger doses than prescribed)
	OVERDSOSE WITHOUT INDICATION OF INTENT	Clinician diagnosis of undetermined intent or insufficient documentation to categorize the case as therapeutic intent, abuse, or self-harm (e.g., patients found unresponsive by paramedics and patients unable or unwilling to provide description of circumstances or intent).
UNSUPERVISED PEDIATRIC EXPOSURE		Access of a medication by a child aged <11 years without caregiver permission or oversight. Most cases involve ingestions or suspected ingestions.
THERAPEUTIC USE		Adverse events from drugs used for therapeutic intent with no indication of misuse. Includes adverse effects, allergic reactions, supratherapeutic effects, medication errors, vaccine reactions, and secondary effects (e.g., choking on a pill)
SELF-HARM/SUICIDE		Clinician diagnosis of self-harm or suicide attempt or documented intent to kill or injure oneself using medications

7.4 APPENDIX D: LITERATURE REVIEW SEARCH STRING

Literature Review Search String

((((((((((((((((((((“Analgesics, Opioid”[Mesh]) OR (“Analgesics, Opioid/administration & dosage”[MeSH Major Topic]) OR (Analgesics, Opioid/adverse effects[MeSH Major Topic]) OR (Analgesics, Opioid/therapeutic use[MeSH Major Topic])) OR ((Oxymorphone [TIAB]) OR (Opana ER [TIAB]) or (Opana IR [TIAB]) or (Oxycontin [TIAB]) or (Oxycodone ER [TIAB])) OR (((opioid[TIAB]) OR (narcotic[TIAB])))) **AND** ((“Prescription Drug Misuse/statistics & numerical data” [MeSH Major topic]) OR (“Substance-Related Disoders” [MeSH]) OR (“Opioid-Related Disorders” [MeSH]) OR (“Drug Overdose”[MeSH]) OR (substance abuse [tiab] OR “nonmedical”[tiab] OR “nonmedical”[tiab] OR “misuse”[tiab] OR “abuse”[tiab] OR “risk factors” [tiab]))) **AND** ((Children[Title]) OR ((Adolescents[Title]) OR (Adolescence[Title]) OR (“Young Adult” [Title])) OR (Pediatric [Title]))) **AND** (Pediatrics [MeSH] OR (Child, Preschool [MeSH]) OR (Child [MeSH]) OR (Adolescent[MeSH]) OR (Infant [MeSH])) NOT (Pregnancy OR Postpartum[MeSH Major Topic])) AND Humans[MeSH Terms]) AND English[Language]) AND ("2010/01/01"[Date - Entrez] : "2019/06/15"[Date - Entrez])))
NOT (autobiography[tiab] OR bibliography[tiab] OR biography[tiab] OR books[tiab] OR "case reports" [tiab] OR "clinical conference"[tiab] OR "clinical trial"[tiab] OR "phase I"[tiab] OR "phase II"[tiab] OR "phase III"[tiab] OR comment[tiab] OR "consensus development"[tiab] OR "controlled clinical trial"[tiab] OR editorial[tiab] OR interview[tiab] OR news[tiab] OR newspaper[tiab] OR "patient education handout"[tiab] OR OR "randomized controlled" [tiab] OR "randomised controlled"[tiab] OR “case series”[tiab] OR “case-series”[tiab] OR webcast[tiab] OR OR Autobiography[ptyp] OR Bibliography[ptyp] OR Biography[ptyp] OR pubmed books[filter] OR Case Reports[ptyp] OR Clinical Conference[ptyp] OR Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Comment[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR Controlled Clinical Trial[ptyp] OR Dictionary[ptyp] OR Directory[ptyp] OR Editorial[ptyp] OR OR Guideline[ptyp] OR Historical Article[ptyp] OR Interactive Tutorial[ptyp] OR Interview[ptyp] OR Legislation[ptyp] OR OR News[ptyp] OR Newspaper Article[ptyp] OR Review[ptyp])))
NOT (“opiate substitution treatment” [mesh] “palliative care” [mesh] OR “terminally ill”[mesh] OR “cancer pain” [mesh] OR “naloxone” [mesh] OR “constipation/chemically induced”[mesh] OR “constipation/diagnosis” [mesh] OR “constipation/epidemiology”[mesh] OR “constipation/psychology”[mesh] OR “analgesia, epidural”[mesh]))

7.5 APPENDIX E: LITERATURE STUDIES INCLUDED IN PRIMARY REVIEW: RISK OF ADVERSE OUTCOMES FOLLOWING THERAPEUTIC OPIOID USE IN PEDIATRIC POPULATIONS

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
Main Articles								
2015	Austic	Age and Cohort Patterns or Medical and Nonmedical Use of Controlled Medication Among Adolescents	Journal of Addiction Medicine	Cross-sectional	SSLS 2009-2013: Middle and High school students from Detroit between 12-18 years and completed at least one survey (N=5,185)	Lifetime nonmedical use of prescription opioids (NMUPO)	Adolescents who received their first prescription opioid prior to age 12 initiated NMUPO than 2 times earlier with respect to OA (adjusted HR=2.02; 95 CI: 1.08-3.75), adjusted for gender, race/ethnicity, and parent/guardian's educational attainment. Peak risk of NMUPO was observed at age 16.	Reported first medical opioid use could be invalid if it occurred much earlier than time of survey.
2019	Bell	Long-term Prescription Opioid Utilization, Substance Use Disorders, and Opioid Overdoses after Adolescent Trauma	Journal of Trauma and Acute Care Surgery	Descriptive/ Case Series- Exposure Only	Patients between ages 12-18 admitted to either one adult or pediatric trauma center (N=736) between 2011-2013	SUD diagnosis or opioid overdose claim	Over the 5 years of follow-up 14% of trauma patients received a SUD diagnosis, and 8% trauma patients had an overdose. Alcohol positivity and drug use at the time of hospital admission was associated with an increased risk of both opioid overdose and SUD diagnosis upon follow-up ($p<0.001$).	97% of patients received prescribed opioid at time of discharge. Exposed vs. non-exposed not compared
2019	Chatterjee	Non-fatal opioid-related overdoses among adolescents in Massachusetts	Drug and Alcohol Dependence	Descriptive/ Case Series- Outcome Only	Statewide All Payer Claims Database (APCD), Prescription Monitoring Program (PMP), Ambulatory Trip Records, Acute Hospital Case Mix for individuals ages	Non-fatal opioid overdose	Only 11% of adolescents experiencing a non-fatal opioid overdose had a documented prescription for opioids within the previous 12 months, compared to 43% of adults.	Only included population that experienced outcome of interest.

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
Main Articles								
					11 and older (N=22,506, n=195 adolescents)			
2018	Chung	Outpatient Opioid Prescription for Children and Opioid-Related Adverse Events	Pediatrics	Prospective Cohort Study	Tennessee State Medicaid recipients ages 2 to 17 years enrolled in Medicaid from 1999 to 2014 (Annual Mean=401,972; Opioid Rx=1,362,503)	Adverse event, defined as ED visit, hospital admission, or death related to opioid adverse effect.	The incidence of opioid related adverse events was 38.3 per 100,000 (95 C.I. 34.9-42.1). The adjusted IRR for adolescents was 2.22 (95 CI 1.67-2.96), adjusting for sex, age, calendar year, days since prescription, current vs. recent use, and prescribed dose. Adverse events occurred more frequently shortly after the prescription fill within 7 days and with increasing dose. For children ages 2-5 and 6-11, 80.4% and 94.4% of AE circumstances were related to therapeutic use. For adolescents, 64.2% were related to therapeutic use. In 96.4%, 97.2%, and 85.2% of opioid-related AEs the source of the opioid was the patient's prescription for ages 2-5, 6-11, and 12-17, respectively. 23% of AEs in adolescents resulted in hospitalization or care escalation, higher than for younger children.	Medical records unavailable for 22.2% of potential cases, so these were not included in analysis. Outcome likely undercounted.
2016	McCabe	Adolescent context of exposure to prescription opioids and substance use	Pain	Longitudinal Cohort	MTF High School Seniors (1976-1996) followed up until age 35: N=4,072	NMUPO and SUD. SUD based on 2+ symptoms of AUD, CUD, and other	Past year prevalence of NMUPO at age 35 was 2.4% among those reporting no opioid use at age 18, 4.4% among those reporting	**AOR adjusted for these variables:** Respondent sex,

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
Main Articles								
		disorder symptoms at age 35: A national longitudinal study				DUD based on DSM 4 or 5 criteria.	medical opioid use, 8.4% for those reporting medical use and NMUPO, and 5.8% among those reporting NMUPO only at age 18. Individuals who indicated lifetime medical use of OA at age 18 had higher odds of past year NMUPO at age 35 compared to those who did not reported any lifetime use of OAs at age 18 (AOR=1.74; 95 CI 1.10-2.76, p<0.05). The risk of NMUPO at age 35 was higher among high school seniors who reported NMUPO only (AOR=2.09; 95 CI 1.10-3.96) or both lifetime medical use and NMUPO (AOR=3.22; 95 CI 1.93-5.36) compared to non-users. Individuals who indicated NMUPO only at age 18 had the highest odds of 2+ SUD symptoms. No differences in the odds of future SUD were found for adolescents who indicated only medical use of OA compared to those who reported no previous OA use.	race/ethnicity, geographical location, urbanicity, parental education, annual alcohol, marijuana, and/or other drug use, and baseline cohort year.
2013	McCabe	Medical Use, Medical Misuse, and Nonmedical Use of Prescription Opioids: Results from a Longitudinal Study	Pain	Longitudinal Cohort	2009-2011 SSLS (n=2,050 7^{th}-11^{th} graders)	Past-year use; nonmedical use; DAST-10 score and CRAFFT score for AUD or DUD	Nearly 8%, 4%, and almost 3% of students who reported having used prescription opioids medically in the first year reported misusing or abusing their own prescription, using someone else's prescription	Results were calculated by cross-tabulating year 1 and year 2 responses, with no

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
Main Articles								
							opioid analgesics for pain relief and using someone else's prescription opioid analgesics for other reasons, respectively, in the second year. Among students who did not use any prescription opioids in the first year, 2%, 1.7%, and 1.3% reported subsequent medical misuse, NMUPO for pain relief, and NMUPO for reasons, respectively. Medical users of prescription opioids in year 1 were not at higher odds of screening positive for alcohol or drug related problems in year 2 compared to non-users, after adjusting for sex, race/ethnicity, school district, and grade level.	adjustment for potential confounders.
2017	McCabe	Trends in Medical and Nonmedical Use of Prescription Opioids Among US Adolescents: 1976-2015	Pediatrics	Trend Analysis/Cross-Sectional	1976-2015 MTF High School Seniors (Yearly sample size range: 2,181-3,791)	NMUPO	Medical use rates were found to be a predictor for the increase in NMUPO. Most adolescents indicating NMUPO also had a history of medical use of prescription opioids. Among those who report a history of both medical and nonmedical use of NMUPO, the most prevalent pattern was medical use before initiating NMUPO.	NMUPO assessed only in adolescence
2019	McCabe	A Prospective Study of nonmedical use of Prescription opioids during adolescence	Drug and Alcohol Dependence	Longitudinal Cohort	MTF High School Seniors (1976-1996) followed up until age 35: N=8,373	SUD based on 2+ symptoms of AUD, CUD, and other	Past year NMUPO was associated with SUD at age 35, particularly those who reported nonmedical use	**AOR adjusted for these variables:** Respondent's

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
Main Articles								
		and subsequent substance use disorder symptoms in early midlife				DUD based on DSM 4 or 5 criteria.	of 2 or more prescription opioids (AOR=2.24; 95 CI 1.54-3.27). Adolescents who indicated medical use of prescription opioids only were not at increased risk of AUD, CUD, ODUD, and other SUD symptoms at age 35 (AOR=1.12; 95 CI: 0.895-1.39). Adolescents who reported medical use of PO before initiating NMUPO were less likely to have SUD symptoms at age 35 than those who initiated NMUPO prior to medical use or those engaged in NMUPO only. Experimental nonmedical use of POs (1-2 times in past lifetime) not associated with AUD or CUD but was significantly associated with other DUD symptoms at age 35 (DUD AOR:2.08, 95 CI=1.23-3.49).	sex, race/ethnicity, geographic location, urbanicity, parental education, annual alcohol, marijuana, or other drug use, and baseline cohort year.
2015	Miech	Prescription Opioids in Adolescence and Future Opioid Misuse	Pediatrics	Cohort	MTF 1990-2012 (n=6,220 who answered questions in at least one of the three follow-up panel surveys)	Past year NMUPO at follow-up	Among 12th graders with little experience with illegal drug drug use and who strongly disapprove of illegal drugs, a legitimate opioid Rx predicts opioid misuse after HS (RR 1.33 95 CI: 1.04-1.7), adjusting for past marijuana use and disapproval of use, cigarette smoking, prescription opioid and/or sedative misuse, binge drinking, sex, school grades, race/ethnicity,	

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
Main Articles								
							and having a parent with a college degree.	
2019	Schroeder	Association of Opioid Prescriptions from Dental Clinicians for US Adolescents and Young Adults with Subsequent Opioid Use and Abuse	JAMA Internal Medicine	Cohort	Optum Research Database-Claims for privately insured patients between ages 16 and 25 years (Exposed=14,888, Non-Exposed=29,776)	1) Healthcare encounter with an ICD-9 or ICD-10 diagnosis code associated with opioid abuse 2) Opioid abuse hospitalization 3) Opioid related death	Opioid use at 90-365 days after dental prescription occurred in 6.9% in the index dental opioid cohort compared with 0.4% in the nonexposed cohort. Filling an opioid analgesic prescription from a dentist was associated with a 5.3% (CI: 5.0%-5.7%) absolute increase in risk of a healthcare claim for opioid abuse, adjusted for patient race/ethnicity and history of non-opioid substance use. Hospitalizations associated with a diagnosis of opioid abuse were more common in the opioid-exposed cohort than in the nonexposed cohort (0.5% vs. 0.3%). Individuals aged 22 to 25 were less likely 16 and 18 to opioid related abuse (AOR 0.8; 95 CI 0.7-1.0), adjusting for age, sex, race/ethnicity, geographic region, and previous diagnosis of nonopioid substance use. Previous nonopioid substance use associated with increased odds of opioid abuse diagnosis (AOR 4.5; 95 CI 3.4-5.9), adjusting for age, sex, race/ethnicity, geographic	Did not examine risk of outcomes among those prescribed opioids by other, non-dental clinicians

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
Main Articles								
							region, and previous diagnosis of nonopioid substance use.	
Supporting Articles								
2015	Cerda	Nonmedical Prescription Opioid Use in Childhood and Early Adolescence Predicts Heroin Use in Young Adulthood: A National Study	Journal of Pediatrics	Cross-Sectional	NSDUH respondents between 12 and 21 years from 2004-2011: N=223,534	Age of initiation of heroin use and heroin use	Prior history of NMUPO associated with heroin initiation (HR 13.12, 95 CI 10.73-16.04) Adjusted HR for heroin initiation based on NMUPO age 10-12 (HR 17.77; 95 CI:13.0-24.3); age 13-15 (HR 15.42; 95 CI: 12.33-19.11); age 8-9 (HR 14.79; 95 CI 6.67-32.77)	**Hazards Model adjusted for the following:** Other substance use different from nonmedical use of prescription opioids before initiation of heroin use, prior use of alcohol, age, sex, income, metropolitan statistical area (MSA), and year of survey.
2019	Kelley-Quon	Association of Nonmedical Prescription Opioid Use with Subsequent Heroin Use Initiation in Adolescents	JAMA Pediatrics	Longitudinal Cohort	Survey data for 9^{th}-12^{th} grade respondents from 10 High Schools in Los Angeles from October 2013- July 2017 (N=3,298, followed up semiannually)	Past 6-month heroin use	Current and prior NMUPO was association with heroin initiation (Current HR 3.18: 95 CI 1.68-6.02; Prior HR 2.09: 95 CI 1.14-3.83). Current NMUPO was more strongly associated with subsequent heroin use compared to of other substances, including cannabis, alcohol, cigarettes, or other nonopioid drugs.	**Hazards Model adjusted for the following:** Prior or current use of alcohol, cigarettes, cannabis, and other substances

Abbreviations: CI, 95% Confidence Interval

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

Drug Utilization Review

Date:	August 21, 2019
Drug Use Analyst:	Daniel Bak, PharmD Division of Epidemiology II (DEPI)
Team Leader:	LCDR Travis Ready, PharmD, MS and Rajdeep Gill, PharmD DEPI
Deputy Division Director:	LCDR Grace Chai, PharmD DEPI
Subject:	U.S. Outpatient Utilization Patterns of Single-Ingredient Oxycodone, Immediate-Release and Extended-Release Products: Pediatric Advisory Committee Meeting
Drug Name:	OxyContin (oxycodone hydrochloride, extended-release)
Application Type/Number:	NDA 022272
Applicant/Sponsor:	Purdue Pharma L.P.
OSE RCM #:	2018-908

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review provides drug utilization patterns of OxyContin (oxycodone extended-release) among pediatric patients <17 years of age in the U.S. outpatient retail pharmacies from 2013-2018. In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA), the Office of Surveillance and Epidemiology (OSE) evaluated pediatric patient drug utilization patterns for OxyContin. The findings of this review will be discussed at the Pediatric Advisory Committee (PAC) meeting in September 2019.

OxyContin (oxycodone extended-release) was originally approved in 1995 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. Subsequently, in 2015 OxyContin (oxycodone extended-release) was also approved to include pediatric labeling in opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

We analyzed U.S. outpatient retail pharmacy utilization patterns of single-ingredient oxycodone ER as well as IR products to provide a comprehensive review of oxycodone use in pediatric patients during the study-period from 2013-2018. In 2018, an estimated 419,000 patients of all ages received dispensed prescriptions for oxycodone ER from U.S. outpatient retail pharmacies. Pediatric patients 11-<17 years of age accounted for approximately 0.1% (400 patients) of the total, followed by patients <11 years of age with less than 0.1% (100 patients). Similar proportions were observed for previous years during the examined period. Pediatric patients who received dispensed prescriptions for oxycodone IR appear to be increasing over the study-period to an estimated 68,000 patients 11-<17 years of age and 63,000 patients <11 years of age in 2018. Based on U.S. office-based physician survey data, oxycodone IR was mainly mentioned in association with diagnoses for the management of sickle-cell disorders among pediatric patients 11-<17 years of age. However, there were no diagnoses data reported for oxycodone ER suggesting infrequent use in pediatric patients during 2013-2018.

Postmarketing Requirements (PMRs) were also issued with the approval for the pediatric population. PMR 2931-2 requires the Sponsor to evaluate OxyContin drug utilization in children aged 17 years and younger. The analyses will evaluate use patterns across all settings of care: number of prescriptions, number of unique patients, patient demographics, initial dose and dosing changes, initial strength, opioid tolerance status at start of therapy, duration of therapy, and conditions for which OxyContin was dispensed. The protocol was finalized May 2018 and the final PMR report is due March 2020.

1 INTRODUCTION

This review provides drug utilization patterns of OxyContin (oxycodone extended-release) among pediatric patients <17 years of age in the U.S. outpatient retail pharmacies from 2013-

2018. In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA), the Office of Surveillance and Epidemiology (OSE) evaluated pediatric patient drug utilization patterns for OxyContin.

1.1 PRODUCT INFORMATION

OxyContin (oxycodone hydrochloride, extended-release), is an opioid agonist indicated in adults 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.[1]

Oxycodone products have been marketed in the U.S. since the 1950s, and OxyContin has been marketed in the U.S. since 1995. The current formulation of OxyContin was approved in 2010. In 2010, the tablets were reformulated with properties designed to make them less easily compromised by tampering (i.e., chewing, crushing, or dissolving).

On August 13, 2015, OxyContin, was approved for use in opioid-tolerant pediatric patients 11 years of age and older, who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent – the same indication as adult patients.

OxyContin extended-release tablets are supplied in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablets for oral administration. Starting August 14, 2014, authorized generics[1] of OxyContin were approved. These are marketed under synonymous names to oxycodone extended-release and are currently supplied in all the same strengths OxyContin is available in.[2]

This review was triggered by the OxyContin approval for pediatric patients in 2015. OxyContin has not been previously presented to the Pediatric Advisory Committee.

1.2 POSTMARKETING REQUIREMENTS (PMRS)

FDA's expansion of OxyContin's approval to the pediatric population required two PMRs: enhanced pharmacovigilance (ePV) (PMR 2923-1) and a drug utilization study (PMR 2923-2).

PMR 2923-1 requires the sponsor analyze post-marketing spontaneous adverse events in children < 17 years of age involving respiratory depression, accidental injury, overdose, misuse, accidental exposure, and medication errors. The status of PMR 2931-1 is discussed in a separate review by FDA's Division of Pharmacovigilance.

[1] An authorized generic is the same as the brand-name drug but does not use the brand name on the label. The authorized generic may have a different color or marking, may be marketed by the brand name company, or another company with the brand company's permission, and may be sold at a lower cost.[2]

PMR 2931-2 evaluates OxyContin drug utilization in children aged 17 years and younger. The analyses will evaluate use patterns across all settings of care: number of prescriptions, number of unique patients, patient demographics, initial dose and dosing changes, initial strength, opioid tolerance status at start of therapy, duration of therapy, and conditions for which OxyContin was dispensed.

The protocol was finalized May 2018 and the final PMR report is due March 2020. The sponsor is still working on providing results for some data elements:

1. Robust results for opioid tolerance status among pediatric patients starting OxyContin therapy
2. Indication among inpatient and outpatient use
3. Patterns of inpatient use

We did not include the results in this review as they are still in progress—the final report is due March 2020.

2 METHODS AND MATERIALS

2.1 DRUG UTILIZATION DATA

We used proprietary drug utilization databases available to the Agency to conduct these analyses. Detailed descriptions of the databases are included in the **Appendix A.**

2.1.1 Data Sources Used

IQVIA, National Sales Perspectives™ (NSP) database was used to determine the settings of care where single-ingredient oxycodone ER and IR products were sold from manufacturers to the various channels of distribution in the U.S. for 2018.

IQVIA, Total Patient Tracker™ (TPT) database was used to determine the estimated number of unique patients who received dispensed prescriptions for single-ingredient oxycodone ER and IR, stratified by patient age (<11 and 11 to <17 years) from U.S. outpatient retail pharmacies from January 2013 through December 2018.

The Syneos Treatment Answers™ database was used to determine the top diagnoses associated with the use of single-ingredient oxycodone ER and IR, stratified by patient age (<11, 11 to <17 years) from January 2013 through December 2018, cumulative.

3 RESULTS

3.1 DRUG UTILIZATION

3.1.1 Settings of Care

In 2018, approximately 60% of single-ingredient oxycodone ER and IR sales were distributed to outpatient retail pharmacies, followed by 40% to non-retail pharmacies, and 1% to mail-order/specialty pharmacies.[2] As a result, we focused our efforts only on the U.S. outpatient retail pharmacy setting.

3.1.2 Patient Data from U.S. Outpatient Retail Pharmacies

Table 1 below shows the nationally estimated number of patients who received dispensed prescriptions for oxycodone ER and IR from U.S. outpatient retail pharmacies from 2013 through 2018. The total number of patients who received dispensed prescriptions for oxycodone ER decreased from an estimated 938,000 patients in 2013 to 467,000 patients in 2018. Pediatric patients 11-<17 years of age decreased from an estimated 2,000 patients in 2013 to 400 patients in 2018. Very few patients aged <11 years received a dispensed prescription for oxycodone ER during the study period. On contrary, patients who received dispensed prescriptions for oxycodone IR increased from an estimated 3.6 million patients in 2013 to 4.6 million patients in 2018. The increase in oxycodone IR use was observed in patients of all ages. Pediatric patients 11-<17 years of age increased from an estimated 35,000 patients in 2013 to 68,000 patients in 2018 and pediatric patients <11 years of age increased from 27,000 patients in 2013 to 63,000 patients in 2018.

2. IQVIA, National Sales Perspectives™. 2018. Extracted April 2019. File 2018-908 NSP Oxycodone ER BPCA.xlsx.

Table 1. Estimated number of patients who received dispensed prescriptions for single-ingredient oxycodone IR and oxycodone ER, stratified by age* (<11, 11-<17 and ≥17 years), From U.S. outpatient retail pharmacies, January 2013 through December 2018.

	2013		2014		2015		2016		2017		2018	
	Patient (N)	Share (%)	Patient (N)	Share (%)	Patient (N)	Share (%)	Patient (N)	Share (%)	Patient (N)	Share (%)	Patient (N)	Share (%)
Total Oxycodone SI	**4,143,318**	**100.0%**	**4,562,525**	**100.0%**	**4,920,197**	**100.0%**	**5,098,015**	**100.0%**	**4,951,019**	**100.0%**	**4,887,085**	**100.0%**
Oxycodone IR	3,609,002	87.1%	4,071,401	89.2%	4,480,483	91.1%	4,719,067	92.6%	4,651,762	94.0%	4,642,327	95.0%
<11 years	26,534	0.7%	42,134	1.0%	48,792	1.1%	67,060	1.4%	67,549	1.5%	63,303	1.4%
11 to <17 years	35,204	1.0%	46,694	1.1%	53,156	1.2%	64,240	1.4%	65,847	1.4%	67,640	1.5%
≥17 years	3,418,688	94.7%	3,830,989	94.1%	4,306,057	96.1%	4,575,549	97.0%	4,499,424	96.7%	4,497,621	96.9%
Unspecified age	299,223	8.3%	265,410	6.5%	80,553	1.8%	5,847	0.1%	35,098	0.8%	12,998	0.3%
Oxycodone ER	937,836	22.6%	894,299	19.6%	821,237	16.7%	719,943	14.1%	581,041	11.7%	466,799	9.6%
<11 years	59	<0.1%	153	<0.1%	73	<0.1%	83	<0.1%	73	<0.1%	128	<0.1%
11 to <17 years	1,908	0.2%	2,188	0.2%	1,221	0.1%	1,277	0.2%	815	0.1%	401	0.1%
≥17 years	907,026	96.7%	864,783	96.7%	814,322	99.2%	719,427	99.9%	579,525	99.7%	465,202	99.7%
Unspecified age	91,224	9.7%	62,998	7.0%	11,144	1.4%	776	0.1%	5,493	0.9%	1,118	0.2%

Source: IQVIA, Total Patient Tracker™. 2013-2018. Extracted July 2019. File: 2018-908 TPT Oxycodone complete age groups 8-1-19.xlsx.

Of note, there are changes in the underlying data and methodology of the proprietary database IQVIA NPA to account for a dynamic pharmaceutical market, including a change to manage prescription claims that are voided or reversed, prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017, data prior to January 2017 have not been adjusted to the new methodology. In 2018, an estimated 2% of total prescription claims for opioid analgesics dispensed from U.S. retail pharmacies appears to have been voided or reversed.

*Note: Patient age groups are inclusive of all patients up to the day before their next birthday.

3.1.3 Survey Data from Office-Based Physicians

An analysis of the top diagnoses associated with the use of single-ingredient oxycodone ER and IR as reported by U.S. office-based physician surveys from January 2013 through December 2018 was conducted (**Table 2)**. No data on diagnoses associated with single-ingredient oxycodone ER use in pediatric patients were reported during the study-period. For pediatric patients aged 11-<17 years, oxycodone IR was most frequently mentioned in association with diagnoses for the management of sickle-cell disorders. However, the number of reports captured for oxycodone use in the pediatric population was very low.

Table 2. Diagnoses associated with the use of single-ingredient oxycodone IR and oxycodone ER as reported by U.S. office-based physician surveys from January 2013 through December 2018, cumulative

	January 2013-December 2018		
	Uses N (000)	Share (%)	95% Confidence Interval (000)
Total Oxycodone Single-ingredient	**35,338**	**100.0%**	**34,161 - 36,516**
Oxycodone IR	**26,756**	**75.7%**	**25,731 - 27,780**
<11 years	41	0.2%	1 - 81
S93 Dislocation and sprain of joints and ligaments at ankle, foot & toe	21	50.0%	<0.5 - 49
M25 Other joint disorder, not elsewhere classified	21	50.0%	<0.5 - 49
11 - <17 years	61	0.2%	12 - 110
D57 Sickle-cell disorders	23	37.7%	<0.5 - 53
M19 Other and unspecified osteoarthritis	12	19.8%	<0.5 - 34
Z09 Encounter for followup exam after treatment for conditions other than malignant neoplasm	9	15.4%	<0.5 - 29
J35 Chronic diseases of tonsils and adenoids	9	15.4%	<0.5 - 29
S80 Superficial injury of knee and lower leg	7	11.6%	<0.5 - 24
≥ 17 years	25,861	96.7%	24,854 - 26,868
Unspecified age	793	3.0%	617 - 970
Oxycodone ER	**8,582**	**24.3%**	**8,002 - 9,163**
<11 years	–	–	–
11 - <17 years	–	–	–
≥ 17 years	8,164	95.1%	7,598 - 8,730
Unspecified age	418	4.9%	290 - 546

Source: Syneos Health Research & Insights LLC, TreatmentAnswers™. 2013-2018. Data extracted August 2019. File: PDDA_2018-908_Oxy_IR_ER_product_age_ICD_10-3_8-20-19.xls

4 DISCUSSION

The Division of Epidemiology conducted this review to provide outpatient drug utilization patterns of oxycodone ER as well as oxycodone IR among pediatric patients <17 years of age from 2013-2018. Our analyses suggest low pediatric use of oxycodone ER from 2013 through 2018, including a downward trend in pediatric use of oxycodone ER after the approval of the pediatric indication in 2015. On the contrary, we observed an increase in the use of oxycodone IR for patients of all ages during the time examined.

Findings from this review should be interpreted in the context of the known limitations of the databases used. Our results can only be generalized to the U.S. outpatient retail setting and not to other important settings where these products are used, such as hospital and mail-order/specialty pharmacies. The patient estimates provided in this review may not sum exactly due to patients aging during the study period and may be counted more than once in the individual age categories or time periods. Consequently, summing patients across patient age groups and time periods will result in overestimates or underestimates of patient counts.

We determined the top diagnoses associated with single-ingredient oxycodone by using survey data from a sample of over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. There were no diagnoses mentioned in association with oxycodone ER use among pediatric patients which is suggestive of infrequent use in pediatric patients. The data were reported in terms of "drug uses" to refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a dispensed prescription. Rather, the term indicates that a given drug was mentioned during an office visit. These data are provided as national estimates, “drug use mentions” lower than 100,000 comprised a sample size too small to provide a reliable national estimate of use.

5 CONCLUSION

In this review, utilization of single-ingredient oxycodone ER and IR dispensed prescriptions was examined in pediatric patients to provide contextual background for the advisory committee meeting discussion. Our analyses suggest that despite the addition of the pediatric indication in August 2015, the use of oxycodone ER remains low in 2018 with less than an estimated 200 patients aged <11 years and 400 patients aged 11 to <17 years.

6 APPENDICES

6.1 APPENDIX A. DATABASE DESCRIPTION

IQVIA, National Sales Perspectives™: Retail and Non-Retail

IQVIA, National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of eaches and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. Estimates provided in this review are national estimates, but statistical tests were not performed to determine whether statistically significant changes occurred over time or between products; therefore, all changes over time should be considered approximate. In addition, these results cannot be validated through medical chart reviews.

IQVIA, Total Patient Tracker™ (TPT)

IQVIA, Total Patient Tracker™ (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year. In addition, the estimates may not sum exactly due to patients aging during the study period and may be counted more than once in the individual age categories or time periods. The projected national estimates are derived from prescription claims from a sample of pharmacies and will include fractional patients or prescriptions due to the methodologies used; therefore, summarization of these results may lead to differences due to rounding. For these reasons, summing patients or prescriptions across patient age groups and time periods is not advisable and will result in overestimates or underestimates of patient or prescription counts. Of note, the estimated prescription and/or patient counts provided are parameter estimates based on projections of sample prescription claims data; therefore, some degree of uncertainty is present in these estimates. These estimates are not intended to be representations of exact enumerations and should be interpreted with caution, particularly if they are based on a small sample size. In addition, the data cannot be validated due to lack of access to medical records in the data sources.

Due to the changing pharmaceutical marketplace, IQVIA has implemented changes to its prescription database to manage prescription voids, reversals, and abandonments that span multiple weeks. Beginning in January 2019, IQVIA has projected published prescription volumes dispensed from the retail pharmacies based on sold date, instead of date of adjudication

(i.e., fill date). Projected estimates have been adjusted and restated in the database back to January 2017, data prior to 2017 remain unadjusted. As a result, a trend break occurs between 2016 and 2017 prescription volumes dispensed from the retail pharmacies, any changes over time must be interpreted in the context of the changes in the underlying data and methodology.

Syneos Health Research & Insights, LLC., Treatment Answers™

Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns. Diagnoses obtained from physician survey data are expressed as "drug uses" which refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. According to Syneos, any number of drug occurrences reported below 100,000 constitutes a sample size too small to provide reliable national estimates of use.

7 REFERENCES

1. OxyContin (oxycodone hydrochloride extended-release) [package insert]. Stamford, CT: Purdue Pharma L.P.; December 16, 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022272s034lbl.pdf. Accessed June 4, 2019.

2. FDA Listing of Authorized Generics [intranet]. FDA internet website. Last updated March 28, 2019. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm126389.htm. Accessed June 4, 2019.

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

Pediatric Postmarketing Pharmacovigilance Review

Date:	September 3, 2019
Safety Evaluator:	Chaitali Patel, PharmD, BCPS Division of Pharmacovigilance II (DPV)
Medical Officer:	Ivone Kim, MD, FAAP DPV
Team Leader:	Neha Gada, PharmD, BCPS DPV
Deputy Division Director:	Ida-Lina Diak, PharmD, M.S. DPV
Product Name:	OxyContin (oxycodone hydrochloride extended-release)
Pediatric Labeling Approval Date:	August 13, 2015
Application Type/Number:	NDA 022272
Applicant/Sponsor:	Purdue Pharma L.P.
OSE RCM #:	2018-908

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for OxyContin in pediatric patients through age 16 years. In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for OxyContin in pediatric patients.

OxyContin was first approved in 1995 and has been available in the present reformulated version since 2010. 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. The approved pediatric labeling is for opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone orally or its equivalent for at least two days immediately preceding dosing with OxyContin.

We evaluated all U.S. pediatric (ages 0 to <17) postmarketing adverse event reports with a serious outcome for OxyContin in the FAERS database from August 13, 2015, approval date of the pediatric labeling, through December 31, 2018. Of the 89 reports reviewed, only eight cases, primarily in the 11 to <17 year age group, mentioned prescribed OxyContin use for post-surgical pain management (n=3) or pain management associated with a medical condition (n=5). Six of these cases reported the subsequent development of drug addiction. Overall, the most frequently reported adverse events in the 11 to <17 year age group are drug addiction and drug abuse, and in the 0 to <11 year age group are overdose and accidental exposures.

DPV did not identify any new safety signals or increased severity or frequency of any labeled adverse events attributable to OxyContin use in the pediatric population. We plan to continue routine pharmacovigilance of OxyContin.

1 INTRODUCTION

This review evaluates FAERS reports for OxyContin in pediatric patients through age 16 years. The Office of Surveillance and Epidemiology (OSE) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious U.S. adverse events associated with OxyContin in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

1.1.1 Product Information and Dosing

OxyContin (oxycodone hydrochloride, extended-release), is an opioid agonist indicated in adults 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.[1]

Oxycodone products have been marketed in the U.S. since the 1950s, and OxyContin has been marketed in the U.S. since 1995. The current formulation of OxyContin was approved in 2010. In 2010, the tablets were reformulated with inactive ingredients intended to make the tablet more difficult to manipulate for abuse.

On August 13, 2015, OxyContin, was approved for use in opioid-tolerant pediatric patients 11 years of age and older, who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

OxyContin extended-release tablets are supplied in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablets for oral administration. Starting August 14, 2014, authorized generics[2] of OxyContin were approved. These are marketed under synonymous names to oxycodone extended-release and are currently supplied in all of the same strengths as OxyContin.[2]

This review was triggered by the OxyContin approval for pediatric patients in 2015. OxyContin has not been previously presented to the Pediatric Advisory Committee.

1.1.2 Clinical Studies[1]

The safety and efficacy of OxyContin have been established in pediatric patients ages 11 to <17 years. Use of OxyContin is supported by evidence from adequate and well-controlled trials with OxyContin in adults as well as an open-label study in pediatric patients ages 6 to <17 years. However, there were insufficient numbers of patients less than 11 years of age enrolled in this study to establish the safety of the product in this age group.

The safety of OxyContin in pediatric patients was evaluated in 155 patients 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. Patients were started on a total daily dose ranging between 20 mg and 100 mg depending on prior opioid dose. The most frequent adverse events observed in pediatric patients were vomiting, nausea, headache, pyrexia, and constipation.

1.1.3 Postmarketing Requirement (PMR)

FDA's expansion of OxyContin's approval to the pediatric population required two PMRs: enhanced pharmacovigilance (ePV) (PMR 2923-1) and a drug utilization study (PMR 2923-2).[3]

PMR 2923-1 requires that the sponsor analyze post-marketing spontaneous adverse events in children <17 years of age involving respiratory depression, accidental injury, overdose, misuse, accidental exposure, and medication errors. The sponsor submitted four ePV interim reports, collectively encompassing the reporting periods from August 13, 2015 through October 12, 2018. The final comprehensive analysis required under this PMR has been received by the FDA and is currently under evaluation.

PMR 2923-2 evaluates OxyContin drug utilization in children aged 17 years and younger. The status of PMR 2923-2 and OxyContin drug utilization analyzes are discussed in a separate review by FDA's Division of Epidemiology (DEPI) II Drug Utilization Analysis team.

1.2 SELECTED LABELED SAFETY ISSUES

Respiratory depression, accidental ingestion, overdose, misuse, neonatal opioid withdrawal syndrome (NOWS) following prolonged transplacental exposure, and life-threatening or fatal events in the setting of concomitant use of central nervous system depressants, (e.g. other opioids), are known risks of all opioid analgesics, including OxyContin. These risks are prominently labeled[1] as a Boxed Warning and in the WARNINGS AND PRECAUTIONS section. The following information is an excerpt from the Highlights of the Prescribing Information section of the OxyContin label:[1]

Warning: Addiction, Abuse and Misuse; Life-Threatening Respiratory Depression; Accidental Ingestion; Neonatal Opioid Withdrawal Syndrome; and Risks From Concomitant Use With Benzodiazepines and Other CNS Depressants

- OxyContin exposes users to risks of addiction, abuse and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions.
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase.
- Accidental ingestion of OxyContin, especially by children, can result in a fatal overdose of oxycodone.
- Prolonged use of OxyContin during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated.
- 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.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

The Division of Pharmacovigilance (DPV) searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS[*] Search Strategy	
Date of Search	April 18, 2019
Time Period of Search	August 13, 2015[†] through December 31, 2018
Search Type	FBIS Product-Manufacturing Reporting Summary
Product Name NDA Verbatim Terms	OxyContin 022272 See **Appendix B** for a list of the verbatim terms searched for authorized generics of OxyContin
Search Parameters	All ages, all events,[‡] all outcomes, worldwide

[*] *See **Appendix A** for a description of the FAERS database.*
[†] *Approval date of pediatric labeling.*
[‡] *Searched using MedDRA version 21.1.*

To maximize the likelihood of evaluating cases of OxyContin and its authorized generics we excluded cases that did not clearly specify OxyContin or an oxycodone *extended-release* product either as a suspect product or in the narrative text.

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from August 13, 2015 to December 31, 2018 with OxyContin. This FAERS data also overlaps with the data submitted for PMR 2923-1, which covered the reporting period August 13, 2015 to October 12, 2018.

Table 2. Total Adult and Pediatric FAERS Reports* for OxyContin Reporting an Age (Received by FDA From August 13, 2015 to December 31, 2018)

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	2,655 (1,492)	2,285 (1,130)	541 (302)
Pediatrics (0 to <17 years)	151 (136)‡	140 (128)‡	33 (31)‡

* May include duplicates and transplacental exposures, since these have not been assessed for causality.
† 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.
‡ We identified two U.S. reports of pediatric deaths among reports not reporting an age and they are included in these counts.

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

Our FAERS search retrieved 128 U.S. serious pediatric reports from August 13, 2015 to December 31, 2018. After accounting for duplicate reports (n=2) and excluding cases that did not clearly specify OxyContin or an oxycodone extended-release product as a suspect product or in the narrative text (n=37),[a] we reviewed 89 U.S. pediatric FAERS cases of OxyContin and authorized generics. Herein, we refer to OxyContin and its authorized generics collectively as "OxyContin."

3.1.3 Characteristics of the Pediatric Cases

Appendix C contains a line listing of the 89 U.S. FAERS cases reporting a serious outcome.

Table 3 summarizes the descriptive case characteristics of the 89 FAERS cases of OxyContin in U.S. pediatric patients reporting a serious outcome received by FDA from August 13, 2015 to December 31, 2018, stratified by age.

[a] In our search of the FAERS database, we searched for OxyContin and verbatim terms for oxycodone extended-release as a suspect product; however, OxyContin and oxycodone extended-release products were sometimes referred to in the narrative text as "oxycodone."

Table 3. Descriptive Case Characteristics of the Serious, U.S. OxyContin Pediatric Cases, Received by the FDA From 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
Serious Outcome‡	Death	4	9
	Life-threatening	4	1
	Hospitalization	3	1
	Disability	1	0
	Congenital anomaly	0	1
	Other serious	66	18

* Transplacental exposure cases.

† These cases were primarily reported by health care providers, and in the 11 to <17 year old group, the cases describe intentional overdoses (i.e., suicide attempts) whereas the cases in the 0 to <11 year old group describe accidental exposures. These cases identify the postmarketing studies as "opioid-overdose validation," "opioid misuse, abuse, questionnaire," and "Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS)-OxyContin."

‡ 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. Cases may have more than one outcome.

Table 4 summarizes the OxyContin cases further by prescribed use and lists the reported reasons for OxyContin use.

Table 4. Evaluation of Prescribed Use and Reasons for Use of OxyContin Among the Serious, U.S. OxyContin Pediatric Cases, Received by the FDA From 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**
	Suspected to be prescribed†	5	0
	No	21	3
	Taken from a family member or residence	*6*	*0*
	Given to by a family member, friend, coach, or "someone"	*10*	*3*
	Mentioned not prescribed	*5*	*0*
	Not specified/other	34	18
	Accidental exposure	*0*	*7*
	Transplacental exposure	*0*	*5*
	Unknown	*34*	*6*
Reported Reason for Use	**Pain, cancer-related**	**1**	**1**
	Pain, non-cancer related/ unspecified pain	**11**	**0**
	Post-operative pain (back, hernia, knee)	*3*	*0*
	Nephrolithiasis‡	*2*	*0*
	Shoulder pain	*2*	*0*
	Knee pain	*1*	*0*
	Migraine	*1*	*0*
	Unspecified pain	*2*	*0*
	Other	**43**	**17**
	Drug abuse/misuse	*40*	*1*
	Intentional overdose	*3*	*0*
	Accidental exposure	*0*	*7*
	Intentional administration to a child	*0*	*4*
	Transplacental exposure	*0*	*5*
	Unknown	**12**	**4**

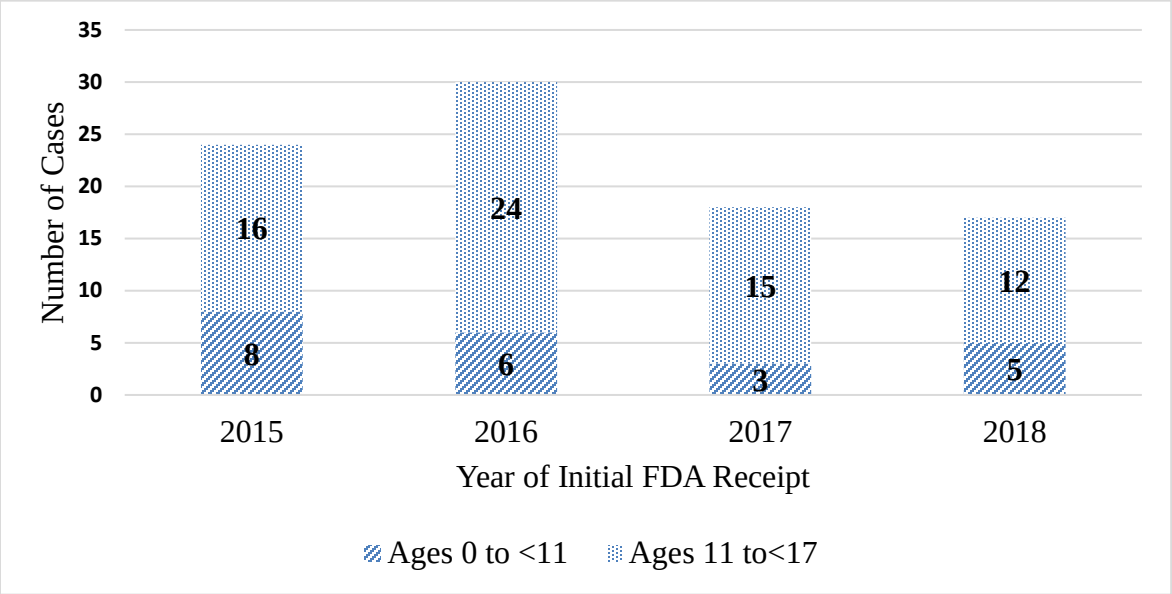
* All eight cases of prescribed use lacked information to assess opioid tolerance. Opioid tolerance is defined for the pediatric indication in the OxyContin labeling: opioid tolerant for at least 5 consecutive days prior and receiving 20 mg per day or more of oxycodone or equivalent in the two days immediately preceding dosing with OxyContin.

† 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).

‡ The cases did not mention if the patients underwent nephrolithotomy.

We note, the majority (12/13) of the prescribed and suspected prescribed use of OxyContin cases in FAERS were identified in the 11 to <17 year old children.

Figure 1. Serious Pediatric Cases for OxyContin by Year of FDA Receipt, from August 13, 2015* to December 31, 2018 (n=89)



* Date of pediatric approval

We did not identify any notable trends in reporting.

3.1.4 Summary of Fatal Pediatric Cases (N=13)

3.1.4.1 Ages 11 to <17 years (n=4)

These deaths are described in the setting of drug abuse or intentional overdose, (i.e., suicide), and describe findings consistent with opioid overdose. Among these four fatal cases, there is a lack of detail stating or suggesting prescribed use. The adverse events described in these cases include the following: death, drug abuse, polysubstance abuse, accidental drug overdose, intentional drug overdose, unresponsive to stimuli, respiratory arrest/apnea, pulmonary edema, and abnormal behavior.

3.1.4.2 Ages 0 to <11 years (n=9)

The median age is 2 years (range, 0 to <11 years). Among these cases only one describes prescribed use. A 10 year old, taking OxyContin and morphine sulfate for pain associated with cancer subsequently passed away due to neoplasm progression. Among the eight remaining cases, two describe accidental exposure to OxyContin, five cases describe overdose involving OxyContin, of which, three cases are suspected to be from intentional administration by family members and two did not specify how the child obtained the OxyContin, and one case describes transplacental exposure to “drugs, ” including OxyContin, which resulted in stillbirth.

Most of the cases (8/9) are sourced from news media and as such generally lack sufficient detail to make meaningful assessments about the overall safety regarding OxyContin, (e.g.,

circumstance by which the child obtained the medication, whether the product was stored in a tamper resistant container, access to other licit and illicit products). Overall, the adverse events described in the cases include the following: death, unresponsive to stimuli, respiratory arrest, dyspnea, somnolence, and malaise.

3.1.5 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=76)

3.1.5.1 Ages 11 to <17 years (n=63)

Among these 63 cases, only 7 report the prescribed use of OxyContin. The reasons for use are tonsillectomy, knee surgery, hernia repair, pain management for cancer pain, a shoulder injury following a sports injury, nephrolithiasis, and [unspecified] cancer pain. The adverse events reported include drug addiction (n=6) and lack of effect (n=1) for the treatment of the teenager's chronic debilitating pain. Of the remaining 56 cases, 54 are drug abuse-related, 1 involves OxyContin misuse, and 1 reports intentional overdose. Overall, the adverse events described in the cases include the following: drug abuse, drug addiction, drug overdose, somnolence, malaise, and drug withdrawal.

All but one of the 54 abuse-related cases are sourced from the news media and as such they generally lack sufficient detail to make meaningful assessments of the adverse event. The adverse events among all the abuse-related cases are primarily drug addiction, drug abuse, and overdose. Among these 54 abuse-related cases, five cases do not explicitly report prescribed use but mention the patient took or started OxyContin for various reasons for use related to pain (post-operative pain management for back surgery and pain management for nephrolithiasis, migraine pain, knee pain, and unspecified, non-cancer pain) and subsequently developed an opioid addiction.

Overall, we were able to note some event characteristics from the narratives; however, it was from a limited number of cases. Of the 63 cases, 6 report the route of abuse (insufflation n=5 and intravenous n=1) without any clinical sequelae reported, 28 report the source of initial OxyContin leading to their addiction [prescribed use n=7, suspected to be prescribed use n=5, taken from someone (e.g., family member) n=6, received from friend/relative n=10], and 7 cases report their OxyContin abuse progressed to heroin use. Overall, most cases report OxyContin use in the context of drug abuse but they lack granularity (e.g., information about OxyContin prescription use or reason for initial use, dose, route, frequency, concomitant drugs) for further assessment.

A representative case from the news media is described below:

> FAERS case #11648481 reports a 16 year old female began taking OxyContin that was prescribed to her mother. The patient became "hooked" and later started using heroin. The case did not provide any additional details, including other concomitant drugs, doses,

route, frequency, details surrounding the event, or clinical outcome from opioid addiction.

3.1.5.2 Ages 0 to <11 years (n=13)

The median age is 1 year (range, 0 to 8 years). We did not identify any cases of prescribed use in this age group. Rather, we identified cases of drug abuse, including intentional administration by a family member to the child, overdose, accidental exposure, and transplacental exposure. The adverse events described in the cases include: unresponsive to stimuli, decreased respiratory rate, overdose, hypoxia, somnolence, groggy, pale, and neonatal opioid withdrawal syndrome (NOWS).

One case sourced from the news media describes drug abuse; a 7 year old snorting OxyContin. In another news media report, a 2 year old was given OxyContin and marijuana by family members. The adverse events are not provided in either case.

Two cases describing drug overdose lack case detail to determine how an 8 month old and 5 year old obtained the OxyContin.

The five accidental exposure cases are from postmarketing study reports (n=5). The cases provide minimal information regarding the studies from which these cases were being reported. Four of the five state "opioid-overdose validation study" and were all initially received by the FDA in the fourth quarter of 2015 and one case states "validation of prescription opioid misuse, abuse questionnaire" and was initially received in the third quarter of 2016. It is unclear if these are from the same study. The median age is 1 year (range, 1 to 8 years). Only three cases report how the three children obtained the OxyContin – from the mother's supply, the grandmother's purse, and grandmother's pillbox. It is unknown whether a tamper resistant container was being utilized.

In total there are four non-fatal U.S. cases of OxyContin describing transplacental exposure. All of the cases lack sufficient information to causally assess the transplacental exposure of OxyContin to the reported adverse event(s) and are confounded by the concomitant medications listed. These cases describe one or a combination of [unspecified] health and behavioral issues, [unspecified] learning disabilities, [unspecified] developmental impacts at an unspecified time later in life, high palate and ankyloglossia. A representative case is described below:

> FAERS case #13693423 reports a male neonate exposed to illegal drugs namely OxyContin, oxycodone, Roxicodone (oxycodone), Percocet (oxycodone/acetaminophen), and hydrocodone in utero, who was diagnosed with neonatal abstinence syndrome (NAS), today conventionally referred to as NOWS, after birth. It was reported he spent 14 or 19 days in the Neonatal Intensive Care Unit (NICU). After an unspecified amount of time, he continued to suffer from numerous health and behavioral issues plus learning disabilities. No other

case details were provided, including the specific health and behavioral issues, learning disabilities, and his and his mother's full medical and drug history.

4 DISCUSSION

DPV analyzed all U.S. pediatric postmarketing adverse event reports with a serious outcome for OxyContin in the FAERS database from August 13, 2015 to December 31, 2018. Of the 89 cases in pediatric patients in the case series, there were no new safety signals identified. All of the adverse events described among these 89 cases are labeled and no increased severity or frequency of any labeled adverse events was appreciated. Among the 13 OxyContin cases evaluated with an outcome of death, the majority of the cases describe the death in the context of drug abuse, overdose, or accidental exposure.

Only eight cases, all but one in the 11 to <17 year age group, mentioned prescribed OxyContin use for post-surgical pain management (n=3) or pain management associated with a medical condition (n=5). Of note, six of these eight cases identified the prescribed use for pain management as the precipitating event that led to drug addiction. Overall, these cases lack information (e.g., medical, drug, and social histories) necessary to characterize potential risk factors, to assess opioid tolerance status, and determine whether subsequent OxyContin use included ongoing prescriptions or if it was illicitly acquired. We inferred five additional cases may also portray prescribed OxyContin use, although it was not explicitly stated, because these cases mention the patient initiated OxyContin to treat pain secondary to medical conditions. Similar to some of the prescribed use cases, these five cases also describe the subsequent development of drug addiction.

The remaining 76 cases did not mention prescribed use and some cases report illicit drug acquisition – it's unknown how and where OxyContin is being obtained. Among these 76 cases, the most frequently reported adverse events in the 11 to <17 year age group are drug addiction and drug abuse and in the 0 to <11 year age group are overdoses and accidental exposures. This finding in the 0 to <11 year age group underscores the need for continued education around environmental safety with opioid products. Overall, the adverse events reported are consistent with opioid exposure or overdose and are labeled events. The lack of case details limits our ability to further characterize the adverse events.

Furthermore, the adverse events identified from these 89 pediatric FAERS cases correspond to the adverse events of interest (respiratory depression, accidental injury, overdose, misuse, accidental exposure, and medication errors (included off label uses)) required to be reported under the enhanced pharmacovigilance PMR 2923-1. Interestingly, all 89 FAERS cases were submitted by sponsors – there were no direct consumer or healthcare provider cases submitted to the FAERS database. Approximately 80% of these cases were obtained by the sponsors from news media. The representation of cases from news media within our case series may be a reflection of stimulated reporting surrounding the current opioid crisis. Since the enhanced

pharmacovigilance PMR 2923-1 covered the reporting period August 13, 2015 to October 12, 2018, it is plausible our review of these 89 FAERS cases also included data submitted by the sponsor under this PMR.

5 CONCLUSION

The pediatric safety profile described in the FAERS cases of OxyContin is consistent with the known safety profile and the current labeling. There is no evidence from these data that warrant labeling changes at this time.

6 RECOMMENDATIONS

DPV will continue to monitor all adverse events associated with the use of OxyContin.

7 REFERENCES

1. OxyContin (oxycodone hydrochloride extended-release) [package insert]. Stamford, CT: Purdue Pharma L.P.; December 16, 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022272s034lbl.pdf. Accessed June 4, 2019.

2. FDA Listing of Authorized Generics [intranet]. FDA internet website. Last updated March 28, 2019. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm126389.htm. Accessed June 4, 2019.

3. Hertz S. Supplement-027 Approval Letter: NDA 22272 OxyContin (oxycodone hydrochloride). Division of Anesthesia, Analgesia, and Addiction Products; Office of New Drugs. DARRTS received/communication date: August 13, 2015. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/022272Orig1s027ltr.pdf.

8 APPENDICES

8.1 APPENDIX A. DATABASE DESCRIPTION

FDA Adverse Event Reporting System (FAERS)

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

FAERS data have limitations. First, there is no certainty that the reported event was 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.

8.2 APPENDIX B. PRODUCT VERBATIM SEARCH TERMS UTILIZED IN THE FAERS SEARCH

Product Verbatim Search Terms	
Search Term	**Product Verbatim Terms**
Oxycodone extended release	Oxycodone extended release; oxycodone extended release (oxycodone); oxycodone extended release (oxycodone) (oxycodone); oxycodone extended release 10 mg teva; oxycodone extended release 2 tabs bid; oxycodone extended release 40 mg teva; oxycodone extended release tablet; oxycodone extended release tabs 20 mg endo; oxycodone extended release) (oxycodone) (oxycodone); oxycontin (oxycodone extended release) unknown
Oxycodone extended-release	Oxycodone extended-release

Product Verbatim Search Terms	
Search Term	**Product Verbatim Terms**
Oxycodone ER	Generic oxycodone ER, generic oxycodone ER 20mg, generic oxycodone ER 40mg, generic oxycodone ER 80mg, oxycodone ER; oxycodone ER 10mg endo; oxycodone ER 20 mg endo; oxycodone ER 40 mg endo; oxycodone ER 80 mg teva; oxycodone ER 20 mg endo; oxycodone ER 20mg endo; oxycodone ER (endo); oxycodone ER (mfr: teva); oxycodone ER (oxycodone hydrochloride); oxycodone ER (oxycodone hydrochloride) (unknown); oxycodone ER (oxycodone) (tablets); oxycodone ER (oxycodone) (unknown); oxycodone ER (oxycontin); oxycodone ER - generic; oxycodone ER - teva; oxycodone ER - watson; oxycodone ER -oxycontin-; oxycodone ER 10 mg; oxycodone ER 10 mg endo; oxycodone ER 10 mg teva; oxycodone ER 10mg; oxycodone ER 10mg teva; oxycodone ER 20 mg; oxycodone ER 20 mg endo; oxycodone ER 20 mg, endo; oxycodone ER 20mg teva; oxycodone ER 30mg; oxycodone ER 40 mg; oxycodone ER 40 mg dava; oxycodone ER 40 mg tab endo; oxycodone ER 40 mg tablets – endo pharmaceuticals; oxycodone ER 40mg; oxycodone ER 40mg & 10 mg; oxycodone ER 40mg actavis; oxycodone ER 40mg tablets; oxycodone ER 80; oxycodone ER 80 mg; oxycodone ER 80 mg - purdue pharma; oxycodone ER 80 mg film coated tablets; oxycodone ER 80 mg po tid; oxycodone ER 80 mg tablet; oxycodone ER 80 mg teva; oxycodone ER 80 mg, teva; oxycodone ER 80mg; oxycodone ER 80mg - teva; oxycodone ER 80mg mallinckrodt; oxycodone ER 80mg mallinokrodt; oxycodone ER 80mg purdue; oxycodone ER 80mg tiva; oxycodone ER by endo; oxycodone ER by teva; oxycodone ER endo pharm 20; oxycodone ER endo pharm 20 mg; oxycodone ER ivax pharm 20; oxycodone ER ivax pharm 20 mg; oxycodone ER tablets 80 mg; oxycodone ER(oxycodone hydrochloride); oxycodone ER, 20 mg, endo; oxycodone ERT 40mg (teva); oxycodone HCl extended release oxycodone ER;teva? oxycodone ER 40 mg, 20mg
Oxycodone CR	Apo oxycodone CR; apo-oxycodone CR; apo-oxycodone CR tablets, 5 mg; generic oxycodone CR 40 mg; oxy/naloxone CR tabs vs oxycodone CR tab; oxycodone CR; oxycodone cr 80mg watson labs; oxycodone CR (oxycodone); oxycodone CR (oxycodone) (unknown); oxycodone CR (oxycontin); oxycodone CR (roxane); oxycodone CR (sustained-release tablet); oxycodone CR - oxycontin-; oxycodone CR 10mg ivax/watson; oxycodone CR 20mg tab; oxycodone CR 40 mg; oxycodone CR 40 mg purdue pharma lp; oxycodone CR 40mg endo 6/05; oxycodone CR 40mg endo 9/06; oxycodone CR 80mg; oxycodone CR n/a; oxycodone CR tablets, 40 mg (oxycodone hydrochloride); oxycodone CR tablets, 40mg (oxycodone hydrochloride)

Product Verbatim Search Terms	
Search Term	**Product Verbatim Terms**
Oxycodone slow release	Oxycodone slow release
Oxycodone SR	Generic oxycodone SR 80mg; oxycontin SR; oxycontin SR (oxycodone hydrochloride); oxycontin SR - generic; oxycontin SR 40mg; oxycontin SR-generic

8.3 APPENDIX C. LINE LISTING OF THE U.S. PEDIATRIC CASES WITH A SERIOUS OUTCOME BY AGE GROUP (N=89)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Serious Outcome*
Ages: 11 to <17 years								
1	10/21/2015	11648461	1	US-MUNDIPHARMA DS AND PHARMACOVIGILANCE-USA-2015-0122733	E	13	NR	OT
2	10/21/2015	11648481	1	US-PURDUE PHARMA-USA-2015-0122734	E	16	F	OT
3	10/21/2015	11648595	3	US-PURDUE PHARMA-USA-2015-0125892	E	15	M	OT
4	10/21/2015	11649958	2	US-PURDUE PHARMA-USA-2015-0124752	E	16	M	OT
5	10/21/2015	11649978	1	US-MUNDIPHARMA DS AND PHARMACOVIGILANCE-USA-2015-0124923	E	14	F	OT
6	10/21/2015	11650047	1	US-PURDUE PHARMA-USA-2015-0125835	E	12	F	OT
7	10/21/2015	11650055	3	US-PURDUE PHARMA-USA-2015-0125246	E	14	F	OT
8	10/21/2015	11650065	3	US-PURDUE PHARMA-USA-2015-0125794	E	16	M	OT
9	10/21/2015	11650067	3	US-PURDUE PHARMA-USA-2015-0126047	E	15	F	OT
10	10/21/2015	11650100	2	US-PURDUE PHARMA-USA-2015-0126256	E	16	F	OT
11	10/21/2015	11650126	3	US-MUNDIPHARMA DS AND PHARMACOVIGILANCE-USA-2015-0126552	E	15	M	OT
12	10/21/2015	11650151	3	US-PURDUE-USA-2015-0126681	E	15	F	OT
13	10/21/2015	11650166	3	US-PURDUE PHARMA-USA-2015-0126815	E	16	F	OT
14	12/2/2015	11794879	2	US-PURDUE PHARMA-USA-2015-0127361	E	13	F	OT
15	12/2/2015	11795714	2	US-PURDUE PHARMA-USA-2015-0127681	E	15	F	HO, OT
16	12/17/2015	11844677	2	US-PURDUE PHARMA-USA-2015-0127906	E	16	M	LT, OT
17	1/5/2016	11888629	2	US-PURDUE-USA-2015-0128181	E	14	M	OT
18	1/11/2016	11908066	2	US-PURDUE PHARMA-USA-2016-0128298	E	14	NR	OT
19	2/2/2016	11989349	2	US-PURDUE PHARMA-USA-2016-0128714	E	15	F	OT
20	2/29/2016	12124725	9	US-PURDUE-USA-2016-0129277	E	15	F	OT
21	3/24/2016	12208063	3	US-PURDUE-USA-2016-0129819	E	14	M	OT
22	4/21/2016	12289590	1	US-PURDUE PHARMA-USA-2016-0130397	E	14	F	HO

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Serious Outcome*
23	4/22/2016	12295537	3	US-MUNDIPHARMA DS AND PHARMACOVIGILANCE-USA-2015-0127930	E	14	M	OT
24	4/22/2016	12296008	1	US-PURDUE PHARMA-USA-2016-0128380	E	11	M	OT
25	5/6/2016	12341255	1	US-PURDUE-USA-2016-0130734	E	14	M	OT
26	5/18/2016	12381876	1	US-PURDUE PHARMA-USA-2016-0130952	E	13	F	OT
27	5/25/2016	12404138	1	US-PURDUE-USA-2016-0131085	E	16	M	OT
28	6/30/2016	12519418	1	US-PURDUE PHARMA-USA-2016-0131903	E	15	F	OT
29	7/28/2016	12603671	1	US-NAPPMUNDI-USA-2016-0132465	E	16	F	OT
30	8/1/2016	12611447	1	US-NAPPMUNDI-USA-2016-0132517	E	16	M	OT
31	8/1/2016	12611490	1	US-PURDUE-USA-2016-0132526	E	15	F	OT
32	8/2/2016	12616676	1	US-NAPPMUNDI-USA-2016-0132548	E	16	M	OT
33	8/3/2016 8/23/2016	12619529 12677663	1 1	US-PURDUE PHARMA-USA-2016-0132612 US-BAYER-2016-159888	E	14	F	HO, OT
34	9/19/2016	12758390	1	US-NAPPMUNDI-USA-2016-0133647	E	13	F	OT
35	10/21/2016	12871528	1	US-NAPPMUNDI-USA-2016-0131198	E	16	F	OT
36	10/21/2016	12871590	1	US-MUNDIPHARMA DS AND PHARMACOVIGILANCE-USA-2016-0131410	E	16	M	OT
37	10/21/2016	12871731	1	US-PURDUE PHARMA-USA-2016-0131785	E	16	F	OT
38	10/21/2016	12871864	2	US-NAPPMUNDI-USA-2016-0132205	E	14	M	OT
39	10/21/2016	12872114	2	US-NAPPMUNDI-USA-2016-0133262	E	15	F	OT
40	12/6/2016	13002445	1	US-NAPPMUNDI-USA-2016-0134639	E	15	M	OT
41	1/12/2017	13109512	2	US-MUNDIPHARMA DS AND PHARMACOVIGILANCE-USA-2017-0135786	E	14	F	OT
42	1/18/2017	13124810	1	US-PURDUE-USA-2017-0135828	E	12	M	OT
43	1/27/2017	13158424	2	US-NAPPMUNDI-USA-2017-0136152	E	15	M	DE, LT, OT
44	2/15/2017	13236548	1	US-PURDUE PHARMA-USA-2017-0136636	E	13	M	OT
45	4/21/2017	13468180	2	US-NAPPMUNDI-USA-2017-0135999	E	15	F	OT
46	5/9/2017	13527786	2	US-PURDUE-USA-2017-0138709	E	16	F	OT
47	5/19/2017	13563260	1	US-NAPPMUNDI-USA-2017-0138917	E	15	F	OT
48	5/31/2017	13599483	2	US-NAPPMUNDI-USA-2017-0139127	E	15	F	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Serious Outcome*
49	6/30/2017	13707721	1	US-PURDUE PHARMA-USA-2017-0139665	E	15	F	OT
50	7/6/2017	13721385	1	US-NAPPMUNDI-USA-2017-0139673	E	15	M	OT
51	9/11/2017	13957651	1	US-PURDUE PHARMA-USA-2017-0140666	E	16	F	LT, OT
52	11/1/2017	14149047	1	US-PURDUE-USA-2017-0141404	E	15	F	OT
53	11/9/2017	14174256	1	US-APOTEX-2017AP020773	E	15	F	DS, OT
54	11/16/2017	14195135	1	US-PURDUE-USA-2017-0141568	E	16	F	OT
55	12/22/2017	14317817	1	US-PURDUE-USA-2017-0142094	E	14	M	OT
56	1/25/2018	14440666	1	US-NAPPMUNDI-USA-2018-0142504	E	14	M	OT
57	1/31/2018	14469012	3	US-PURDUE PHARMA-USA-2018-0142559	E	16	M	OT
58	5/1/2018	14833522	1	US-PURDUE PHARMA-USA-2018-0143427	E	16	F	OT
59	6/26/2018	15067198	1	US-NAPPMUNDI-USA-2018-0143991	E	15	F	OT
60	7/10/2018	15127299	1	US-NAPPMUNDI-USA-2018-0144136	E	12	M	OT
61	10/17/2018	15516723	2	US-NAPPMUNDI-USA-2018-0144984	NE	13	NR	OT
62	11/9/2018	15603574	1	US-NAPPMUNDI-USA-2015-0145158	E	14	M	DE, LT, OT
63	11/13/2018	15611229	1	US-NAPPMUNDI-USA-2017-0145172	E	12	F	DE, OT
64	11/13/2018	15613791	1	US-NAPPMUNDI-USA-2017-0145169	E	16	M	DE, OT
65	11/28/2018	15664365	1	US-NAPPMUNDI-USA-2018-0145290	E	15	F	OT
66	11/28/2018	15664366	1	US-NAPPMUNDI-USA-2018-0145288	E	13	M	OT
67	12/18/2018	15734656	1	US-NAPPMUNDI-USA-2018-0145464	E	15	M	OT
Ages: 0 to <11 years								
68	9/30/2015	11576842	2	US-PURDUE-USA-2015-0126471	E	2	M	DE, OT
69	10/9/2015	11617326	1	US-PURDUE-USA-2015-0126557	E	14 months	F	OT
70	10/13/2015	11626673	1	US-NAPPMUNDI-USA-2015-0126650	E	2	M	OT
71	10/13/2015	11626684	1	US-NAPPMUNDI-USA-2015-0126651	E	1	F	OT
72	11/6/2015	11704858	1	US-PURDUE PHARMA-USA-2015-0127181	E	2	F	OT
73	11/24/2015	11773878	1	US-PURDUE PHARMA-USA-2015-0127510	E	Neonate	NR	DE, OT
74	11/25/2015	11777927	2	US-PURDUE-USA-2015-0127556	E	9 months	F	DE

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Serious Outcome*
75	12/31/2015	11882736	1	US-PURDUE-USA-2015-0128169	E	1	M	OT
76	1/26/2016	11956436	1	US-ENDO PHARMACEUTICALS INC.-2016-000509	E	0	M	CA, OT
77	8/2/2016	12616682	1	US-PURDUE-USA-2016-0132613	E	8	M	OT
78	8/16/2016	12657027	4	US-MUNDIPHARMA DS AND PHARMACOVIGILANCE-USA-2016-0132908	E	5	M	DE, OT
79	8/18/2016	12665212	1	US-NAPPMUNDI-USA-2016-0132929	E	2	M	DE
80	8/26/2016 9/2/2016	12690547 12711248	1 1	US-PURDUE PHARMA-USA-2016-0133068 US-PFIZER INC-2016409633	E	5	M	OT
81	11/1/2016	12900459	1	US-NAPPMUNDI-USA-2016-0134445	E	7	M	OT
82	6/12/2017	13644119	1	US-NAPPMUNDI-USA-2017-0139220	E	14 months	M	DE, OT
83	6/27/2017	13693423	4	US-ENDO PHARMACEUTICALS INC-2017-003612	E	0	M	OT
84	10/18/2017	14102357	2	US-ENDO PHARMACEUTICALS INC-2017-005531	E	0	M	OT
85	4/30/2018	14828737	1	US-NAPPMUNDI-USA-2018-0143420	E	8 months	NR	OT
86	5/18/2018	14914874	1	US-PURDUE-USA-2018-0143626	E	10	M	DE
87	7/18/2018	15158517	1	US-ALLERGAN-1833255US	E	0	M	OT
88	11/9/2018	15603766	1	US-PURDUE-USA-2015-0145161	E	2	M	DE
89	11/19/2018	15632838	1	US-NAPPMUNDI-USA-2018-0145217	E	2	M	DE, HO, LT, OT

*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. A case may have more than one serious outcome.
Abbreviations: E= Expedited, NE=Non-Expedited, F=Female, M=Male, NR=Not Reported, DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, CA= Congenital Anomaly, OT=Other medically significant