Opioid Analgesics: Translating Pediatric Study Results into Labeling

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Pediatric Data for Opioid Analgesics

- Pediatric Research Equity Act (PREA) requires an assessment for new drug applications (NDAs) under certain circumstances
- Many opioid analgesic drug products have outstanding PREA requirements
- Studies usually conducted post approval
  - Data submitted as a supplement to the NDA
- Few opioid analgesics have pediatric labeling
  - Many challenges to completing studies
- Risks and benefits to the individual as well as to public health taken under consideration when evaluating proposed pediatric labeling

Opana IR Example

- Opana (oxymorphone hydrochloride) tablets
  - Immediate-release (IR) formulation
  - Indication: management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
  - Approved June 2006
- PREA requirements
  - 0 to <2 years: pharmacokinetics (PK), safety, and efficacy
  - 2 to <17 years: PK and safety
- December 2018 NDA supplement
  - Pediatric data in 2 to <17 year group

Opana IR 2 to <17 Pediatric Program

- Formulations used
  - Marketed Opana IR tablets for 12 to 17 years old
  - Oxymorphone oral solution (1 mg/mL) for 2 to 12 years old

Opana IR 2 to <17 Pediatric Program

- **EN3319-101:** open-label, randomized, single-dose, two-period, two-sequence crossover; 5 mg oral solution vs. Opana 5 mg in fasted healthy adult subjects
  - Formulations are bioequivalent
- **EN3203-010:** open-label, ascending, two-part, single- and multiple-dose evaluation of the safety, pharmacokinetics, and effectiveness of **oxymorphone for acute postoperative pain** in pediatric patients 12 to 17
  - Single and multiple doses: 5 mg, 10 mg, 15 mg
  - Safety population: n=58
- **EN3319-302:** open-label, 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 patients ages 2 to ≤12
  - Single dose: 0.05 mg/kg, 0.1 mg/kg, and 0.2 mg/kg
  - Multiple dose: 0.2 mg/kg
  - Safety population: n=45

Observed PK parameters for pediatrics (dose mg/kg BW) and adults

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

			Cmax (ng/mL)		AUC0-t (ng.h/mL)		AUC0-inf (ng.h/mL)	
Study	Population	Dose	Mean	SD	Mean	SD	Mean	SD
EN3203-101	Adults	5 mg	0.69	0.34	3.94	1.67	4.34	1.86
EN3203-010	>12 to 17 y	5 mg* (0.08 mg/kg)	0.90	0.69	4.57	2.84	5.80	4.08
		10 mg* (0.16 mg/kg)	0.83	0.69	3.77	2.26	10.22[#]	6.52[#]
		15 mg* (0.23 mg/kg)	1.76	1.02	17.01	15.68	18.29	9.10
EN3319-302	6 to ≤12 y	0.05 mg/kg	0.42	0.21	2.56	2.00	2.42	0.052
		0.10 mg/kg	1.14	0.85	3.01	0.77	3.01	0.95
		0.20 mg/kg	1.33	0.77	5.32	4.53	6.92	4.02
	2 to <6 y	0.05 mg/kg	0.33	0.22	1.69	0.94	3.22	1.56
		0.10 mg/kg	1.76	1.62	3.99	2.09	3.69	3.12
		0.20 mg/kg	3.16	1.65	9.37	5.81	14.30	5.01

- *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

Individual Oxymorphone Single-Dose PK Parameters in 12 to 17: All Subjects

Subject ID	Dose (mg)	Body Weight (kg)	Dose by Body Weight (mg/kg)	C_{max}	AUC_{0-t}	AUC_{0-inf}
EN3203-010-0004-1002	5	58.4	0.08562	4.00	20.96	22.262122
EN3203-010-0008-1001	5	66.7	0.07496	0.52	3.61	4.6704245
EN3203-010-0008-1002	5	65	0.07692	0.65	2.00	2.0760854
EN3203-010-0012-1001	5	80.5	0.06211	0.08	1.18	1.597359
EN3203-010-0014-1001	5	93.1	0.05371	0.35	2.96	3.5902727
EN3203-010-0014-1002	5	33.9	0.14749	1.84	6.92	6.9949329
EN3203-010-0014-1003	5	66.4	0.0753	0.52	4.04	5.6234958
EN3203-010-0014-1004	5	63.8	0.07837	1.41	6.14	7.4308224
EN3203-010-0014-1005	5	61.9	0.08078	1.83	9.74	14.441455
EN3203-010-0002-1004	10	79.4	0.12594	0.64	3.35	n/a
EN3203-010-0002-1005	10	74.8	0.13369	0.04	0.12	n/a
EN3203-010-0002-1008	10	58.9	0.16978	1.20	5.11	6.7678845
EN3203-010-0009-1002	10	70.7	0.14144	0.29	2.57	n/a
EN3203-010-0014-1006	10	51.9	0.19268	0.84	6.47	17.742911
EN3203-010-0017-1001	10	53	0.18868	1.96	4.98	6.1583119
EN3203-010-0004-1005	15	45.4	0.3304	0.98	16.64	23.109953
EN3203-010-0004-1006	15	85.4	0.17564	1.33	9.88	17.007165
EN3203-010-0006-1001	15	77.9	0.19255	2.59	24.77	26.115575
EN3203-010-0006-1002	15	81.8	0.18337	2.05	13.82	20.586492
EN3203-010-0014-1007	15	51.1	0.29354	1.97	7.59	28.604918
EN3203-010-0014-1008	15	88.4	0.16968	1.06	7.90	8.7005507
EN3203-010-0017-1002	15	53.4	0.2809	33.55	467.26	746.33646
EN3203-010-0017-1003	15	61.7	0.24311	3.64	52.21	n/a
EN3203-010-0018-1001	15	66	0.22727	0.49	3.30	3.8883495

Study EN3203-010: Patient Disposition

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: Adapted from Sponsor's clinical study report

Safety Findings for Opana IR in 2 to <17

- No deaths
- 7 serious adverse events (SAEs)
  - Largely related to the underlying condition and/or surgical procedure:
    - Atelectasis and fat embolism
    - Failure of spinal implant
    - Anemia, unequal pupils, blurred vision, and headache
    - Neutropenia and postoperative fever
    - Postoperative joint dislocation
    - Abdominal abscess
    - Wound dehiscence
  - All resolved with treatment
- 5 discontinuations due to adverse events
  - Sedation (2), tremor, somnolence, lethargy
  - All resolved spontaneously

Safety Findings for Opana IR in 2 to <17

- Common adverse events
  - Approximately two-thirds of pediatric patients experienced adverse events (AEs)
    - More AEs with multiple-doses than with single-doses
  - Most common AEs (≥5%) for the entire pediatric population included (in order of decreasing reporting frequency)
    - Nausea, pyrexia, constipation, vomiting, pruritus, and headache
  - Next most common AEs included five cases (4%) of each of the following
    - Peripheral edema, oxygen saturation decreased, muscle spasms, dizziness, and urinary retention
  - Generally consistent with post-operative experiences and with the known safety profile of opioid analgesics

Sponsor's Proposed Pediatric Labeling

- Section 6 Adverse Reactions
  - Clinical study safety information for pediatric patients 2 years and older
- Section 8.4 Pediatric Use
  - Description of the safety information from the pediatric studies
- Section 12.3 Pharmacokinetics
  - Include a statement describing that oxymorphone HCl oral solution was bioequivalent to Opana tablets under fasting conditions in adults
  - Include a statement regarding 'similar oxymorphone exposure' as well as the 'half-life' between pediatric patients 2 to 17 years and adults, based on a weight adjusted basis
- Section 14 Clinical Studies
  - Description of the open-label pediatric studies

Risk Benefit Considerations

- Clinical pharmacology review: substantially higher exposures in 2 of 24 patients (~8%) in 12 to 17 age group
  - Considered outliers in the PK analysis
  - 1) 13-year-old female that received a single 5-mg dose and completed the study
    - No AEs reported
    - Pain intensity on a 100-mm visual analog scale (VAS): 50 mm at baseline and generally trended down to 20 mm at the 6-hour time point
  - 2) 14-year-old female that received a single 15-mg dose and discontinued early due to lack of efficacy
    - 3 reported AEs: pruritus, fever, and asthma exacerbation (none reported as serious)
    - Pain intensity on the VAS: 62 mm at baseline to 52 mm at the 6-hour time point; however, scores were variable over the assessment period
- Although these patients did not experience significant safety concerns and the outlier PK data for one may be attributable to an erroneous result, higher than expected drug levels in the general patient population is a potential safety issue

Risk Benefit Considerations

- Extrapolation of efficacy from adults to children down to 2 years of age typically allowed based on demonstrating comparable exposures
- Open-label efficacy data raise concerns about the appropriateness of extrapolation based on PK data for this product
  - Substantial number of patients withdrew due to lack of efficacy in the 12 to 17 group
- Data suggest a higher dose needed to achieve efficacy in pediatric patients
  - No pediatric safety data for higher doses

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