

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022272Orig1s027

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA#/Supplement #	22272/027
Applicant Name	Purdue Pharma
Date of Submission	December 10, 2014
PDUFA Goal Date	June 10, 2015
Proprietary Name / Established (USAN) Name	OxyContin / Oxycodone hydrochloride extended-release tablets
Dosage Forms / Strength	10, 15, 20, 30, 40, 60, 80 mg
Proposed Indication(s)	OXYCONTIN is an opioid agonist indicated for pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in: <ul style="list-style-type: none"> • Adults; and • 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
Action/Recommended Action:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Javier Muniz, MD, John Feeney, MD
Statistical Review	Feng Li, PhD, Freda Cooner, PhD
CMC Review/OBP Review	Zedong Dong PhD, Ramesh Raghavachari, PhD
Clinical Pharmacology Review	Srikanth Nallani, PhD, Yun Xu, PhD Kevin Krudys, PhD
DPMH	Amy Taylor, MD, MHS, Linda Lewis, MD
OSI	John Lee, MD, Janice Pohlman, MD, MPH, Kassa Ayalew, MD, MPH
CDTL Review	John Feeney, MD
OSE/DRISK	Danny S. Gonzalez, PharmD, MS, Joan Blair, RN, MPH, Kim Lehrfeld, PharmD, BCPS, Reema Mehta, PharmD, MPH
DMPP	Morgan Walker, Pharm D, Barbara Fuller, RN, MSN, CWOCN, LaShawn Griffiths, MSHS-PH, BSN, RN,
OPDP	Koung Lee, RPh, MSHS, Samuel Skariah, Olga Salis
Other	

OND=Office of New Drugs
DMEPA=Division of Medication Errors Prevention
CDTL=Cross-Discipline Team Leader
DCDP=Division of Consumer Drug Promotion
DMPP=Division of Medical Policy Programs

OSE= Office of Surveillance and Epidemiology
OSI=Office of Scientific Investigations
OPDP=Office of Prescription Drug Promotion
OMP=Office of Medical Policy Initiatives

Signatory Authority Review Template

1. Introduction

OxyContin is an extended-release formulation of oxycodone that was initially approved December 12, 1995, as 10 mg, 20 mg, and 40 mg tablets, under NDA 20553. An 80 mg tablet was approved January 6, 1997, followed by a 160 mg tablet on March 15, 2000, and 15 mg, 30 mg and 60 mg tablets on September 18, 2006. The Applicant ceased distribution of the 160 mg tablet in April of 2001. The current formulation was approved in 2010 under NDA 22272 and represents a product intended to deter abuse through physicochemical properties that make the tablet difficult to prepare and abuse by the intranasal and intravenous routes of administration.

The Applicant has submitted the current supplement in response to the FDA's Written Request to conduct studies with oxycodone in pediatric patients. The Applicant requested pediatric exclusivity and to gain approval for new labeling for OxyContin that would include additional information from their pediatric studies.

As described by Dr. Feeney and reproduced below, there is a public health need for medications to manage pain in pediatric patients.

Like adults, pediatric patients are subject to the pain of both malignant and non-malignant conditions. Not infrequently, pediatric patients undergo complicated orthopedic procedures that can result in pain lasting weeks to months. In addition, there are a number of painful procedures involved in both the diagnosis and treatment of pediatric medical conditions. Over the last decade, pain in pediatric patients has received increasing attention with a focus on the development of proven analgesics.

To encourage pediatric drug development, the Food and Drug Administration Modernization Act of 1997 was signed into law and established incentives for conducting pediatric studies for drugs for which exclusivity or patent protection exists. In 2002, the Best Pharmaceuticals for Children Act (BPCA) extended the provisions of FDAMA by continuing to offer an additional six months of patent exclusivity for drugs being tested for pediatric use. Later, in 2003, the Pediatric Research Equity Act (PREA) was passed and imposed certain requirements on the sponsors of new drug applications, i.e. a proposed timeline and plan for the submission of pediatric studies. The requirements of PREA are triggered by a new indication, a new dosage form, a new route of administration, a new dosing regimen, or a new active ingredient. Because the reformulated OxyContin was approved while the older formulation was still marketed (and is not considered a new dosage form), the requirements of PREA were not triggered by NDA 22272.

2. Background

This supplemental application was submitted in response to a pediatric written request, initially issued to the Applicant in 1998 and subsequently amended a number of times. The details of the history of the written request are described in the reviews by Drs. Muniz and Feeney. At the time of the original written request, there were no extended-release opioid analgesics approved for use in the pediatric age range and information for the use of immediate-release oxycodone was available in literature, but not in product labeling. The extent of chronic pain in the pediatric age range was not entirely clear, although, at the time, there was less emphasis on the use of extended-release opioid analgesics for chronic pain rather than acute pain as evidenced by the studies initially conducted in support of the NDA for OxyContin.

The final version of the written request called for the Applicant to conduct three studies:

- Study 1: Pharmacokinetic (PK) study of an age-appropriate formulation of oxycodone in opioid-naïve patients from birth up to < 4 years of age.
- Study 2: Efficacy, safety, and pharmacokinetic study of an age-appropriate formulation of immediate-release (IR) oxycodone in opioid-naïve patients from 5 years up to \leq 16 years of age.
- Study 3: Open-label, safety and pharmacokinetic study of an oxycodone extended-release tablet in opioid-tolerant patients from 6 years to \leq 16 years of age.

The Applicant used an immediate-release oral solution formulation for Studies 1 and 2. To address the requirements of the written request for Study 3, and in particular, whether it was possible to study the safety of an extended-release opioid in patients under the age of 17, the Applicant was asked to evaluate whether OxyContin was already being prescribed off-label for pediatric analgesia. The results of this evaluation indicated that the clinical settings for which OxyContin was prescribed for pediatric patients differed somewhat than in adults. Two of the most common reasons for chronic pain in adults, osteoarthritis and low back pain, are very infrequent in children. Rather, OxyContin was being used in pediatric patients treated for pain associated with cancer and pediatric patients undergoing extensive surgical procedures that resulted in the need for opioid analgesics to manage pain for two to four weeks. The protocol for Study 3 was then developed with the plan to enroll patients that were consistent with the existing use. The objective was to provide pharmacokinetic and safety data for prescribers who were treating these pediatric patients, rather than having them continue to rely on shared clinical experience alone.

The written request would look somewhat different if it were to be issued today. Following a 2009 scientific workshop, a publication described a number of issues associated with the use of analgesics for the treatment of pain in pediatric patients. Taking the information discussed and reference articles cited in this publication, it appears reasonable to extrapolate the efficacy of opioid analgesics known in adults to children as young as age 2.¹ Efficacy studies would be

¹ Berde CB, Sethna, NF. Analgesics for the Treatment of Pain in Children. N Engl J Med 2002; 347(14): 1094-

required for patients less than 2 years of age and studies to determine the pharmacokinetic profile and the safety of the opioid analgesic would be required for the entire pediatric age range.

The following table from page 2 of Dr. Nallani's review summarizes the study design of the eight studies submitted in support of this pediatric efficacy supplement. There were five multiple-dose (including studies OXP1005, OXP3003, and OTR3001) and one single-dose pediatric pharmacokinetic and safety studies, two single-dose bioavailability/ bioequivalence (BA/BE) studies in adults, and, a relative oral bioavailability study of the original formulation of OxyContin and immediate-release oxycodone tablets in pediatric patients (Study 0602) from 1998. The following table from page 2 of Dr. Nallani's review summarizes the study design of these studies.

Table: Studies Submitted to support pediatric population PK analysis.

Study (Country)	Study Objective(s)	Study Design	Treatment (Dose, Dosage Form, Route) (Product ID),	No. of Dosed Subjects. (M/F) Type Age: mean (range)
PEDIATRIC				
OTR1020 (United States and Australia)	To characterize the single and multiple dose PK and safety of reformulated OxyContin tablets (OTR) of various strengths in pediatric patients	Multicenter, multinational, open-label, single- and multiple dose	OTR 10, 15 and 20 mg tablets, po [10 mg: CB-2010-03], [15 mg: CB-2010-04], [20 mg: CB-2009-15]	30 (13M/17F) Pediatric patients 13.5 y (9-16y)
OTR3001 (Multinational) WR Study 3	To evaluate safety, efficacy and pharmacokinetics of OTR in opioid tolerant pediatric patients	Multicenter, multi-national, open-labeled, multiple-dose	OTR 10, 15, 20, 30, or 40 tablets, po [*]	155 (66M/89F) Pediatric patients 13.7 (6 to 16y)
OXP1005 (Multinational) WR Study 1	To characterize the PK and safety of oxycodone in pediatric patients following administration of IR oxycodone hydrochloride solution	Multicenter, multinational, open-label, multiple-dose, dose-ranging	Oxycodone HCl oral solution, 0.05 mg/kg, 0.1 mg/kg and 0.2 mg/kg, po [0.05 mg/kg:CB-2002-11], [0.1 mg/kg:CB-2002-11], [0.2 mg/kg:CB-2002-11]	60 (29M/31F) Pediatric patients 1.14y (birth to 4y)
OXP3003 (Multinational) WR Study 2	To characterize the PK and safety of oxycodone in pediatric patients following administration of IR oxycodone hydrochloride solution 0.1 to 0.2 mg/kg q6h	Multicenter, multinational, randomized, double-blind, multiple-dose, dose-ranging	Oxycodone HCl oral solution, 0.1 and 0.2 mg/kg, po [Oral solution: CB-2002-11],	65 (24M/41F) Pediatric patients 11.4y (5 to 16y)
OXP3004 (Multinational)	To evaluate safety and pharmacokinetics of the approved adult conversion ratio (1:1) from immediate release (IR) oxycodone q6h to OC q12h in pediatric patients	Multicenter, multinational, multiple-dose, dose-ranging	Immediate Release 5 mg capsule, po [CB41, DH61] OC 10 mg tablet, po [DR61, EB3N1]	7 (5M/2F) Pediatric patients 12.6y (7 to 16y)
OC96-0602 (United States)	To compare the relative bioavailabilities following single doses of IR oxycodone and OC in children	Single-center, randomized, open-label, two-way crossover, single-dose	OC 10 mg tablet, po [OC C25] Immediate Release 5 mg, po [IR Oxycodone 962438]	13 (7M/6F) Pediatric patients 9.6y (6 to 12y)
ADULTS				
OTR1005 (United States)	To characterize the single-dose PK of oxycodone in healthy subjects and assess bioequivalence of OTR relative to OC	Single-center, randomized, open-label, single-dose, two-way crossover study	OTR 40 mg tablets, po [CB-2006-18] OC 40 mg tablets, po [W66G1]	92 (61M/31F) Healthy adult subjects under fasting and under naltrexone blockade, 31y (18-49y)
OTR1502 (United Kingdom)	To determine the bioequivalence of OTR (UK) and OTR (US) tablets; and bioequivalence of OTR(UK) and OC tablets	Single-center, open-label, multiple-dose, three-treatment, three-period, crossover	OTR (UK), OTR (US) and OC 80 mg tablets, po [OTR (UK) 80 mg: PN3369], [OTR (US) 80 mg: PN3374], [OC 80 mg: PN3350]	24 M Healthy adult subjects under naltrexone blockade, 31y (19-45y)

F=female; IR=immediate-release; M=male; OC= original OxyContin Tablets; OTR=reformulated OxyContin Tablets with abuse-deterrent properties; PK=pharmacokinetic(s); po=per os (by mouth); q12h=every 12 hours; WR=written request; y=years.

* Numerous lots were used in Study OTR3001, which was conducted over a 4-year period. For Product IDs please consult CSR OTR3001.

3. CMC/Device

There were no changes to the currently marketed OxyContin tablets. As noted by Dr. Dong, the focus of the CMC review was whether the Applicant had made (b) (4)

In response to information requests, three technical reports were submitted.

From Dr. Dong's review:

A teleconference was held between FDA and Purdue Pharma L.P. on May 8, 2015. (1) When asked whether a (b) (4)

Based on the information provided by the applicant, it appears that Purdue Pharma (b) (4)

I concur with the conclusions reached by the chemistry reviewer, that the Applicant made a (b) (4). There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted in support of this application.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Nallani reviewed the pharmacokinetic data from all eight studies submitted in support of this supplemental application. The following section has been reproduced from Dr. Nallani's review:

Clinical pharmacology of OxyContin: Pharmacokinetic properties of oxycodone following single and multiple dose administration (10 – 80 mg) of OxyContin (reformulated product approved in 2010) have been fairly well investigated in adults. Dose proportionality has been established for OxyContin 10 mg – 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC). Given the short elimination $t_{1/2}$ of oxycodone (~5 hours), steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OxyContin. Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated O-demethylation to oxymorphone.

Pediatric Studies with OxyContin and Immediate release Oxycodone formulations:

It is important to note most of the pediatric OxyContin studies (in the table above) conducted in support of this supplement recruited pediatric patients with moderate to severe pain who were already receiving oxycodone or other opiates for pain management and could be considered opioid tolerant. These patients were administered OxyContin only if they required at least 10 mg twice daily. Patients requiring less than 10 mg twice daily were not included in the study.

Pharmacokinetics and safety of an age-appropriate oral formulation of immediate release oxycodone solution in opioid-naïve hospitalized patients from birth up to < 4 years of age were evaluated in Study OXP1005 and PK of oxycodone in opioid-naïve hospitalized pediatric patients 6 – 16 yrs. of age in Study OXP3003. (b) (4)

, this review is focused on the use of OxyContin in pediatric patients and is not intended to provide dosing recommendations of this immediate release formulation in the pediatric population.

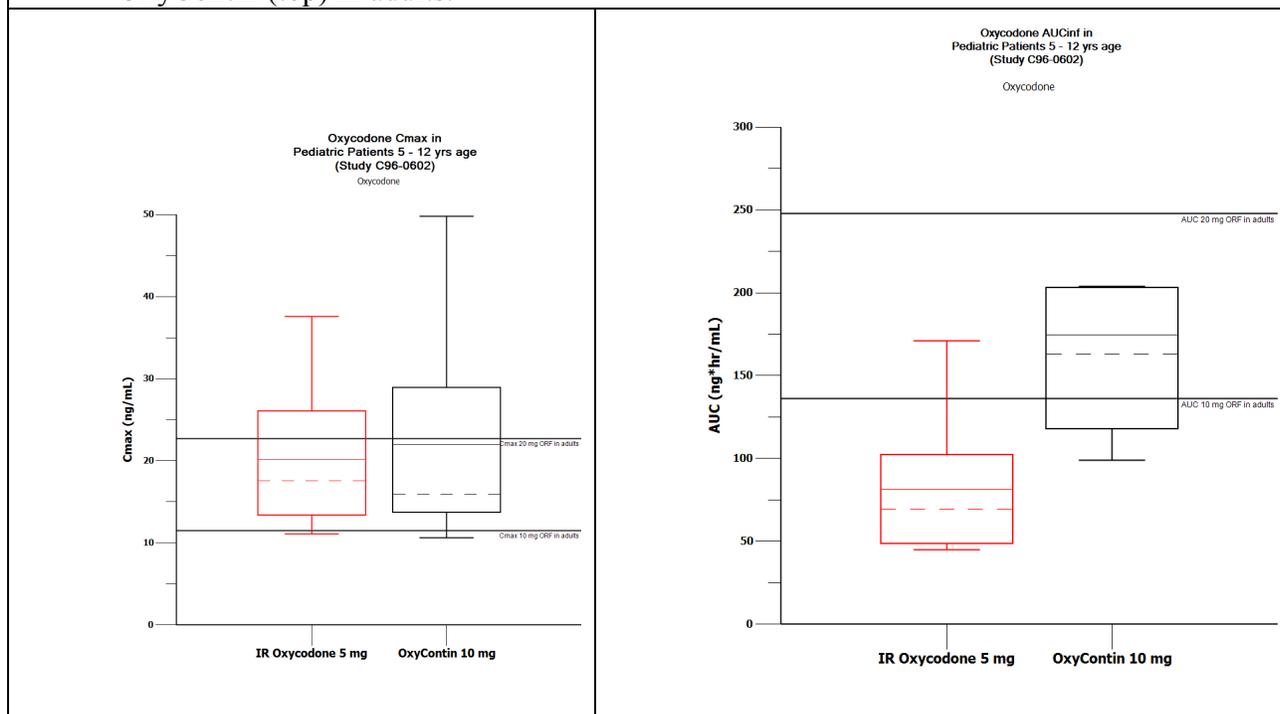
Pediatric Bioavailability Study OC96-0602:

In Study OC96-0602, pharmacokinetics of oxycodone following crossover administration of OxyContin (10 mg original formulation) was compared with IR oxycodone (5 mg tablet). Pediatric patients (N=13) were previously receiving opiates other than oxycodone to qualify for this study. In this study, pediatric patients in the 6-12 yrs. age group receiving 10 mg OxyContin had a C_{max} or peak plasma concentration of oxycodone ~22 ng/mL; where as adults receiving the same dose would have a C_{max} of ~ 11 ng/mL. OxyContin label indicates that a single 10 mg dose produces oxycodone AUC of about 136 ng.hr/mL.

Table: Summary of PK Parameters from Study OC96-0602

PK Metric	Arithmetic Mean (SD)	
	IR Oxycodone (5 mg)	OxyContin® (10 mg)
AUC _t (ng-h/mL)	83.2 (43.0)	201.0 (143.0)
AUC _∞ (ng-h/mL)	81.3 (39.1) ^b	174.6 (91.1) ^c
C _{max} (ng/mL)	20.2 (8.3)	22.0 (13.0)
t _{max} (h)	2.1 (0.9)	3.3 (1.7)
t _{1/2(elim)} (h)	2.6 (1.0) ^c	5.2 (1.8) ^c
MRT (h)	4.2 (1.2)	8.7 (1.9)

Figure: Box-Plot comparing C_{max} (left figure) and AUC (right figure) of oxycodone in pediatric patients of 6 -12 yrs. age following administration of OxyContin 10 mg or IR oxycodone 5 mg (tablet) doses. Horizontal reference lines are label indicated mean C_{max} (left figure) and mean AUC (right figure) of 10 mg OxyContin (bottom) and 20 mg OxyContin (top) in adults.



The observed increase in exposure of oxycodone following OxyContin administration in the 6 -12 year age group is possibly due to decreased metabolic clearance in these patients with lower body weight.

In another pediatric safety study (OTR3001) where OxyContin safety and PK was evaluated in 6 -16 year old patients, it was observed that for any given dose of OxyContin (10 – 30 mg) patients in 6 – 12 yr. age group had higher C_{max} compared to 13 -16 yr. old patients (See appended results for OTR3001). The higher C_{max} appeared to be a more consistent observation in pediatric patients < 60 kg bodyweight compared to >60 kg bodyweight (See figure below). Very limited number of subjects received doses ≥40 mg OxyContin; hence a comparison could not be made. These findings are consistent with the population pharmacokinetic analysis which demonstrated that body weight is an important covariate for the volume of distribution and clearance of oxycodone. A dose-proportional increase in C_{max} and AUC was noted in pediatric patients in each age group or body weight group.

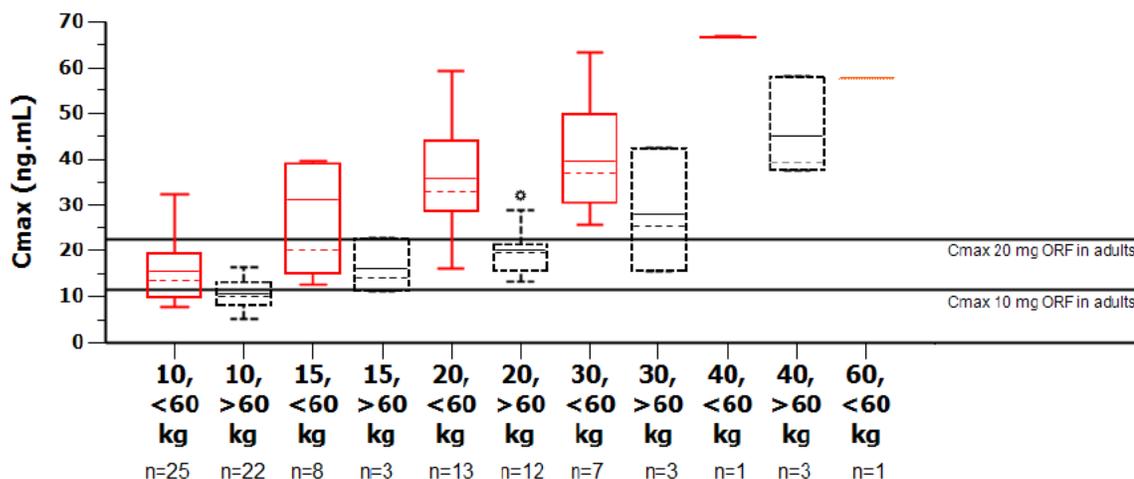
It is important to note most of the pediatric studies conducted in support of this supplement (including study OTR3001) recruited pediatric patients who were already receiving oxycodone or other opiates for pain management and could be considered opioid tolerant. Hence, the observed difference in C_{max} in pediatric patients with lower

age/bodyweight becomes clinically relevant when considering 10 mg OxyContin for opioid naïve patients. In fact, pediatric patients in the age range of 6 – 12 yrs., especially those with lower body weight, might benefit from a 5 mg OxyContin formulation.

(b) (4)

It is noteworthy that pediatric patients 12 – 17 yrs old have similar exposure to oxycodone compared to adults receiving similar dose of OxyContin.

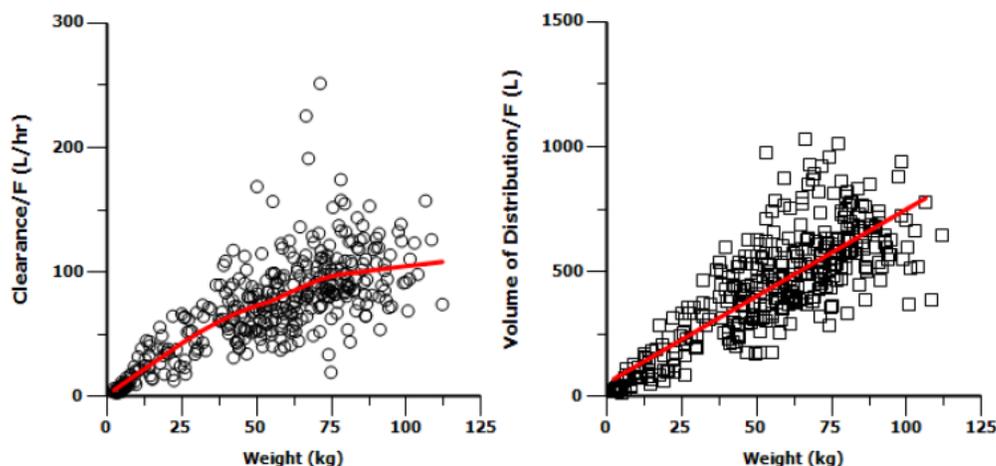
Figure: Box-Plot comparing C_{max} (first dose) of oxycodone in pediatric patients (Study OTR3001) of bodyweight <60 kg vs. >60 kg bodyweight following administration of different OxyContin doses. Horizontal reference lines are label indicated mean C_{max} of 10 mg OxyContin (bottom) and 20 mg OxyContin (top) in adults.



Note: Limited number of patients received doses ≥ 40 mg of OxyContin; hence a comparison could not be made.

Data from several adult and pediatric studies (as indicated above) were combined in a population PK analysis to characterize the population pharmacokinetics of oxycodone in adult and pediatric subjects and to estimate the effects of individual-specific covariate factors, in particular, age and weight on the variability in pharmacokinetics. Full review of the population PK analysis is appended to this memo. The main conclusions of the analysis are discussed below. The final model identified weight as a predictor of variability in clearance (CL/F) and volume of distribution (V/F) and age as a predictor of variability in CL/F in patients less than one year of age. No other covariates investigated demonstrated any relationship in the graphical evaluation of unexplained variability in oxycodone PK.

Figure: A plot of oxycodone clearance against bodyweight of pediatric patients and healthy subjects (Based on final model).



The table below describes clearance and volume of distribution for oxycodone in different bodyweight groups.

Table: Summary statistics of clearance and volume of distribution of oxycodone based on bodyweight groups from all studies.

Weight Group	Variable	N	Mean	SD	Median	Variable	N	Mean	SD	Median
<10 kg	CL/F	43	8.4	4.8	7.2	V/F	43	45.8	26.4	37.6
11-20 kg	CL/F	23	31.2	11.4	31.9	V/F	23	127.4	55.6	117.9
21-60 kg	CL/F	138	66.8	25.2	64.8	V/F	138	388.9	156.6	369.6
>60 kg	CL/F	168	96.7	31.5	91.8	V/F	168	590.4	151.5	584.1

These results provide further support that a 10 mg dose in lighter patients (i.e., less than 10 years of age) would result in higher exposure than the same dose in the adult population. Therefore, pediatric patients would benefit from a 5 mg OxyContin formulation.

We also note that the Sponsor’s pharmacokinetic model has adequately characterized the pharmacokinetics of oxycodone throughout the entire pediatric population. Therefore, this model could potentially be used to derive pediatric dosing regimens of immediate release oxycodone formulation that would match the exposure in adults at dosing regimen of FDA-approved oxycodone products.

I concur with the conclusions reached by the clinical pharmacology reviewer that the pharmacokinetic profile of OxyContin has been sufficiently characterized to support a pediatric indication and the dosing and administration information in the package insert. There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

Based in large part on an understanding of neurodevelopment, the physiology of pain, and the pharmacology of opioid analgesics, as discussed by Berde et al.², it is reasonable to extrapolate a finding of efficacy for oxycodone as an analgesic from adults to pediatric patients over the age of 2 years. There is supportive evidence provided from Study OXP3003, although, as discussed by Dr. Li and presented below, this study was not adequately designed to provide a statistically rigorous assessment of efficacy.

Study OXP3003 was a multicenter, double-blind, randomized, placebo-controlled, dose-ranging study with the primary objectives to the pharmacokinetics and safety of oxycodone hydrochloride oral solution, in opioid-naïve patients, 5 to 16 years of age with moderate to severe acute pain expected to last for at least 2 days. Efficacy was also evaluated in this study.

Patients were stratified by age and randomized in a ratio of 3:3:2 to one of three treatment groups: oxycodone 0.1 mg/kg, oxycodone 0.2 mg/kg, or placebo, to be taken every six hours for 18 to 24 hours. All patients were permitted intravenous patient (or nurse) controlled analgesia with morphine, or oral morphine as needed during the double blind treatment period.

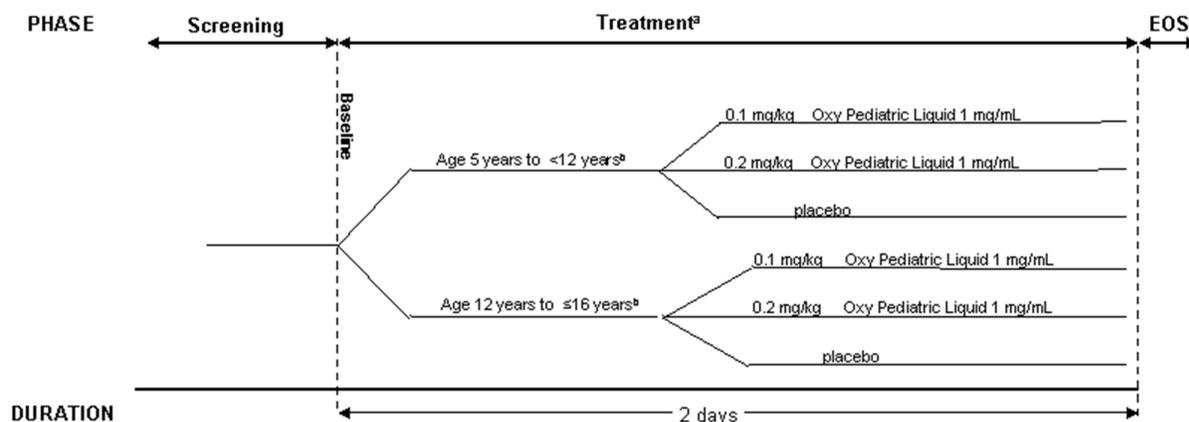


Figure 1. OXP3003 Study Schematic

*EOS= End of Study
(Source: OXP3003 Study Report, Figure 1, page 23)

Details about the inclusion and exclusion criteria and safety monitoring can be found in Dr. Muniz' review (starting on page 33). Patients were to be monitored with continuous pulse oximetry, and oxygen saturation levels and somnolence were to be assessed prior to each dose of study medication. Efficacy assessments included the amount of supplemental pain medication used expressed as IV morphine equivalents, and pain intensity.

Although the study planned to enroll 100 patients, the study was terminated after 68 patients were enrolled. Subjects had pain as a result of a variety of clinical situations including major cardiac or orthopedic surgeries and pain following medical procedures. Overall, 83% of patients completed the study with the greatest number completing from the oxycodone 0.2 mg/kg

² Ibid.

treatment group. Patient disposition is provided in the following table from Dr. Muniz' review. (page 46).

Table 9. Patient Disposition and Reasons for Discontinuation by Age Group: Safety Population. Study OXP3003

Age Group	Oxy Pediatric Liquid 1mg/ml			Total (N = 65)
	Placebo (n = 19)	0.1 mg/kg (n = 24)	0.2 mg/kg (n = 22)	
All Patients				
Completed, n (%)	15 (78.9)	18 (75.0)	21 (95.5)	54 (83.1)
Discontinued, n (%)	4 (21.1)	6 (25.0)	1 (4.5)	11 (16.9)
Adverse event	1 ^a (5.3)	1 (4.2)	0	2 (3.1)
Subject's choice	3 (15.8)	3 (12.5)	1 (4.5)	7 (10.8)
Administrative	0	2 (8.3)	0	2 (3.1)
Age Group: 5 to <12 years	n = 7	n = 10	n = 9	N = 26
Completed, n (%)	6 (85.7)	7 (70.0)	9 (100.0)	22 (84.6)
Discontinued, n (%)	1 (14.3)	3 (30.0)	0	4 (15.4)
Adverse event	0	1 (10.0)	0	1 (3.8)
Subject's choice	1 (14.3)	1 (10.0)	0	2 (7.7)
Administrative	0	1 (10.0)	0	1 (3.8)
Age Group: 12 years to ≤ 16	n = 12	n = 14	n = 13	N = 39
Completed, n (%)	9 (75.0)	11 (78.6)	12 (92.3)	32 (82.1)
Discontinued, n (%)	3 (25.0)	3 (21.4)	1 (7.7)	7 (17.9)
Adverse event	1 (8.3)	0	0	1 (2.6)
Subject's choice	2 (16.7)	2 (14.3)	1 (7.7)	5 (12.8)
Administrative	0	1 (7.1)	0	1 (2.6)

^a Patient experienced a pretreatment-emergent AE (vomiting) before placebo administration.

The extent of exposure was summarized by Dr. Muniz (page 47):

The mean exposure to Oxy Pediatric Liquid was 18.6 hours overall. All patients in the safety population received at least 1 dose, while 91% of patients received at least 2 doses, 89% received at least 3 doses, 86% received at least 4 doses, and 38% received 5 doses.

According to the Applicant’s analyses, a finding of efficacy is supported by the results in the following table from Dr. Muniz review (page 48):

Table 11. Sponsor’s Summary of Efficacy Results. Study OXP3003*

	Dose Interval	Placebo Mean (SD)	0.1 mg/kg Mean (SD)	0.2 mg/kg Mean (SD)	Nominal P value**
PCA Morphine	0 - <6 hours	0.19 (0.15)	0.11 (0.11)	0.11 (0.10)	.083
	Overall, excl 0-<6 hours	0.58 (0.52)	0.25 (0.27)	0.27 (0.30)	.017
	Overall, incl 0-<6 hours	0.69 (0.64)	0.34 (0.35)	0.37 (0.38)	.047
Total Opioid	0 - <6 hours	0.20 (0.16)	0.11 (0.11)	0.12 (0.10)	.096
	Overall, excl 0-<6 hours	0.60 (0.52)	0.27 (0.28)	0.33 (0.35)	.040
	Overall, incl 0-<6 hours	0.71 (0.64)	0.35 (0.36)	0.44 (0.44)	.077
Acetaminophen	0 - <6 hours	0.26 (1.13)	0	0	.096
	Overall, excl 0-<6 hours	5.25 (10.94)	1.44 (3.71)	0.47 (2.14)	.032
	Overall, incl 0-<6 hours	4.68 (10.34)	1.32 (3.57)	0.45 (2.09)	.039
Pain Score	Mean, 0-<6 hours	4.1 (1.37)	3.3 (2.07)	3.1 (2.50)	.034
	Max, 0-<6 hours	6.8 (2.12)	4.8 (2.79)	5.4 (3.05)	.047
	1 hr post dose, excl 0-<6	3.5 (1.30)	2.8 (2.07)	2.8 (2.67)	.038
	1 hr post dose, incl 0-<6	3.9 (1.28)	2.9 (2.02)	3.0 (2.54)	.031
	6 hrs post dose, excl 0-<6	3.5 (1.35)	3.0 (2.27)	3.2 (2.87)	.195
	6 hrs post dose, incl 0-<6	4.2 (1.54)	2.9 (2.23)	3.2 (2.81)	.033
	Mean, Overall	4.1 (1.09)	3.2 (2.00)	3.2 (2.50)	.030
	Max, Overall	7.5 (2.01)	6.0 (2.63)	5.7 (2.97)	.018

*Based on Jonckheere-Terpstra test. Smaller p-values are evidence in favor of nonincreasing dose response.

** One-tailed p-value. Please see efficacy discussion in Section 6 for further details

During the initial six hours, all three groups used similar amounts of supplemental morphine, but subsequently, patients receiving the oral oxycodone required less supplemental morphine. Patients randomized to oral oxycodone had lower pain scores throughout the study.

Dr. Li conducted an analysis of the protocol and results of Study OXP3003 and noted the following (pages 5 and 6):

Neither the protocol nor the Statistical Analysis Plan (SAP) clearly specified the primary or secondary efficacy endpoints for treatment comparisons. The study report presented analysis results for multiple variables evaluating pain scores and supplemental pain medication usage, respectively. A statistical test for dose response was performed on each of these efficacy variables using the Jonckheere-Terpstra approach. No adjustment for multiplicity was planned or performed. The full efficacy analysis population included the 65 patients who received at least one dose of study medication and had at least one subsequent efficacy evaluation. Efficacy outcomes were not collected for the discontinued patients after they stopped the randomized treatment pre-maturely. There was no imputation method proposed for missing efficacy assessments.

Dose response was not established with statistical significance at a one-sided level of 0.025 or two-sided level of 0.05 for most of the efficacy variables. Nevertheless, it was observed that all of these efficacy variables were numerically in favor of oxycodone

against placebo. Patients randomized to placebo reported slightly higher pain on average and used more supplemental pain medications during the study.

In summary, the efficacy study was not prospectively designed or powered to show superiority over placebo, and as such it could not provide evidence of efficacy with the usually required level of statistical significance

I concur with Drs. Muniz and Li that study OXP3003 provides support for a finding of efficacy for the analgesic effects of oxycodone, although not a statistically rigorous assessment. A finding of efficacy for OxyContin is primarily based on extrapolation from adults.

8. Safety

It is not acceptable to extrapolate safety from adults to pediatric patients. The safety database consists of data from Studies OXP1005, OXP3003, OTR3002, OC96-0602, OTR1020, and OTR3004. Study OXP3003 was described above. The remaining studies are described below.

Study OXP1005 was an open-label pharmacokinetic and safety study of immediate-release oxycodone for acute pain for up to two days. Pediatric patients from birth to 4 years of age were enrolled and stratified into three age groups (birth to 30 days, 31 days to ≤ 6 months, and 7 months to ≤ 4 years). Patients received oxycodone oral solution. The study plan was to start with a low dose, 0.05 mg/kg, followed by dose escalation to 0.1 mg/kg and then 0.2 mg/kg and based on an Investigator Steering Committee's review of the patient safety data. Patients were also permitted supplemental oral morphine (0.1 to 0.3 mg/kg q2h) or nurse-controlled analgesia via PCA pumps with morphine sulfate 15 mcg/kg per dose with an 8-minute lockout for a maximum of six doses per hour on an as needed basis, based on an evaluation of pain intensity by the investigator or designated nurse. Details of the study design, conduct, and results can be found in Dr. Muniz' review.

Study OTR3001 was an open-label pharmacokinetic and safety study of OxyContin in pediatric patients from 6 to 16 years of age. This was the only study that provided safety information for the use of OxyContin in pediatric patients. One particular condition of enrollment was that patients must have been receiving at least 20 mg of oxycodone daily for at least the five consecutive days prior to dosing, and no more than 240 mg daily during the last 48 hours before the start of study drug dosing. This is because a 20 mg dose may have been too large for some smaller patients. By having patients initiate opioid treatment according to their healthcare provider's standard approach using an immediate-release opioid prior to initiating treatment with OxyContin, patients could be titrated in increments smaller than 10 mg, the smallest strength of OxyContin. Patients were required to have an expected need for opioid treatment of pain of at least two weeks and up to four weeks. Patients could have been outpatients or inpatients at the time of enrollment and inpatients were to continue in the study upon hospital discharge. Under the supervision of the healthcare team, adjustment of the OxyContin dose up or down as needed for pain management or management of adverse events was permitted. Patients were to be dosed twice daily and asymmetric dosing was permitted. An extension study (OTR3002) permitted continued use of OxyContin and further follow up for patients requiring longer treatment of pain with an opioid analgesic.

A total of 155 patients were enrolled; 134 patients were enrolled at US sites. Nearly all patients were converted to OxyContin from an immediate-release formulation of oxycodone, morphine, hydromorphone, or hydrocodone. Most of the patients enrolled had undergone a major surgical or medical procedure or had cancer. Patients who had undergone surgery were not to be converted to OxyContin until at least five days following surgery.

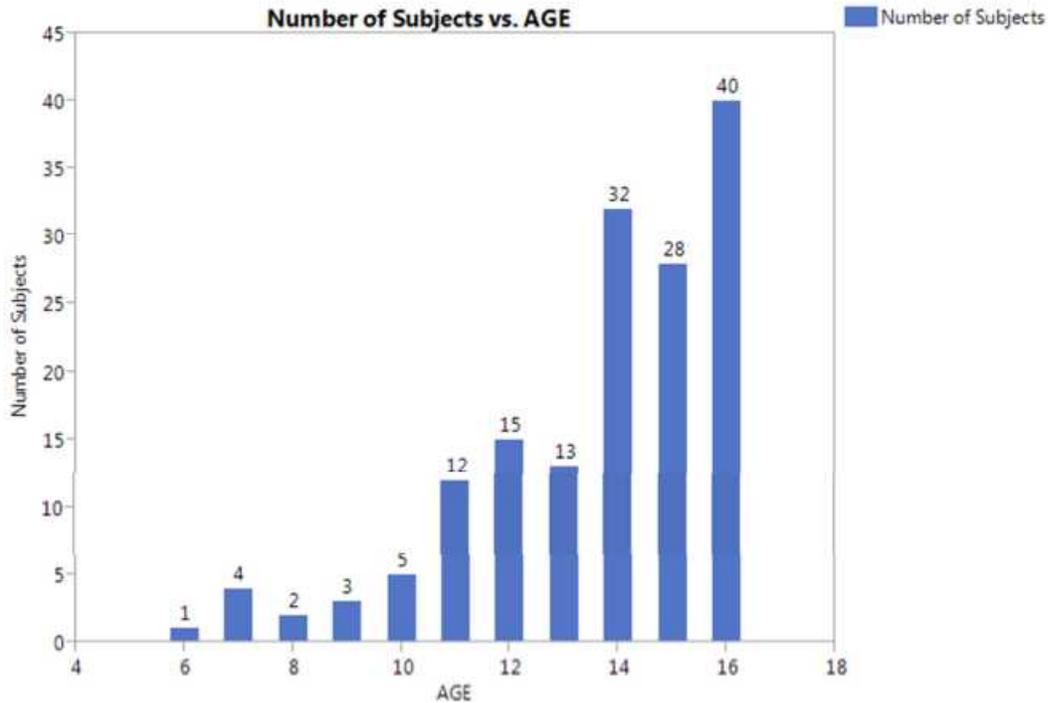
The following table from Dr. Muniz' review (page 62) describes the study population:

Table 15. Demographic and Baseline Characteristics: Safety Population. Study OTR3001

Characteristics	Age Group		Total (N = 155)
	6 to < 12 Years (N=27)	≥ 12 to ≤ 16 Years (N=128)	
Age (y)			
N	27	128	155
Mean (SD)	9.6 (1.65)	14.5 (1.34)	13.7 (2.33)
Median	10.0	15.0	14.0
Min, Max	6, 11	12, 16	6, 16
Sex, n (%)			
Male	13 (48.1)	53 (41.4)	66 (42.6)
Female	14 (51.9)	75 (58.6)	89 (57.4)
Race, n (%)			
White	20 (74.1)	88 (68.8)	108 (69.7)
Black	7 (25.9)	31 (24.2)	38 (24.5)
Asian	0	1 (0.8)	1 (0.6)
Other	0	8 (6.3)	8 (5.2)
Ethnicity, n (%)			
Latino or Hispanic	2 (7.4)	16 (12.5)	18 (11.6)
Not Latino	25 (92.6)	112 (87.5)	137 (88.4)
Tanner Puberty Staging, n (%)			
Stage 1	14 (51.9)	6 (4.7)	20 (12.9)
Stage 2	10 (37.0)	3 (2.3)	13 (8.4)
Stage 3	2 (7.4)	24 (18.8)	26 (16.8)
Stage 4	1 (3.7)	61 (47.7)	62 (40.0)
Stage 5	0	34 (26.6)	34 (21.9)
Screen Weight (kg)			
N	25	128	153
Mean (SD)	38.72 (10.055)	63.21 (18.474)	59.21 (19.587)
Median	39.90	60.00	56.20
Min, Max	24.5, 65.0	26.0, 124.6	24.5, 124.6
Missing	2	0	2
Height (cm)			
N	24	128	152
Mean (SD)	141.71 (13.034)	165.30 (10.241)	161.58 (13.733)
Median	145.60	165.05	162.60
Min, Max	119.0, 158.0	136.0, 190.5	119.0, 190.5
Missing	3	0	3
Body Mass Index (kg/m²)			
N	24	128	152
Mean (SD)	19.08 (2.775)	22.92 (5.639)	22.32 (5.468)
Median	18.57	21.92	21.21
Min, Max	14.2, 27.1	12.2, 44.7	12.2, 44.7
Missing	3	0	3

Although 40% of patients were to have been in the 6 up to 11 age group, only 15 patients less than 11 years of age were enrolled. The remaining 140 patients were 11 and older as demonstrated in the following figure from Dr. Muniz' review (page 64).

Figure 4. Age Distribution Breakdown, Study OTR3001 (N=155)



Patient disposition is provided in the following table from Dr. Muniz’ review (page 70).

Table 18. Patient Disposition and Reasons for Discontinuation: Safety Population. Study OTR3001

Category	Age Group		Total (N=155) n (%)
	6 to < 12 Years (N=27)	≥ 12 to ≤ 16 Years (N=128)	
	n (%)	n (%)	
Completed study	17 (63.0)	105 (82.0)	122 (78.7)
Completed study in ≥2 to <4wks	6 (22.2)	62 (48.4)	68 (43.9)
Completed study in ≥4 ^a	11 (40.7)	43 (33.6)	54 (34.8)
Discontinued study in <2 weeks	9 (33.3)	12 (9.4)	21 (13.5)
AE	3 (11.1)	4 (3.1)	7 (4.5)
Subject’s choice	3 (11.1)	1 (0.8)	4 (2.6)
Lost to follow-up	0	0	0
Lack of therapeutic effect	0	1 (0.8)	1 (0.6)
Confirmed or suspected diversion	0	0	0
Administrative	3 (11.1)	6 (4.7)	9 (5.8)
Discontinued study in ≥2 to <4wks	1 (3.7)	11 (8.6)	12 (7.7)
AE	0	3 (2.3)	3 (1.9)
Subject’s choice	0	3 (2.3)	3 (1.9)
Lost to follow-up	0	1 (0.8)	1 (0.6)
Lack of therapeutic effect	0	4 (3.1)	4 (2.6)
Confirmed or suspected diversion	0	0	0
Administrative	1 (3.7)	0	1 (0.6)

Abbreviations: AE = adverse event; N = number of patients in population groups and total; n = number of patients with data.

^aThere are 2 subjects with extended exposure in OTR3001 because the extension study was not available.

Note: Reasons for discontinuation are based on the End of Study (EOS) eCRF page.

Percentages are based on N.

Approximately 80% of patients completed between two and four weeks, and 54 patients continued for four weeks or longer.

There was a wide range of doses across the study population as presented in the following table from Dr. Muniz' review (page 71).

Table 19. Summary of Extent of Exposure to OxyContin by Age and Overall: Safety Population. Study OTR3001.

Category	Age Group		Total (N=155)
	6 to < 12 years (N=27)	≥ 12 to ≤ 16 Years (N=128)	
Mean Weekly Dose During Study (mg/day)			
n	26	128	154
Mean (SD)	29.75 (13.458)	34.02 (18.260)	33.30 (17.577)
Median	26.80	30.00	29.25
Min, Max	10.0, 67.0	10.0, 140.0	10.0, 140.0
Minimum Weekly Dose During Study (mg/day)			
n	26	128	154
Mean (SD)	17.88 (8.738)	17.50 (11.346)	17.56 (10.925)
Median	15.00	15.00	15.00
Min, Max	10.0, 40.0	10.0, 80.0	10.0, 80.0
Maximum Weekly Dose During Study (mg/day)			
n	26	128	154
Mean (SD)	33.08 (14.972)	41.80 (24.772)	40.32 (23.596)
Median	30.00	40.00	40.0
Min, Max	20.0, 80.0	10.0, 160.0	10.0, 160.0
Number of Days on Therapy			
n	26	128	154
Mean (SD)	20.2 (9.50)	20.8 (8.12)	20.7 (8.34)
Median	24.0	18.0	18.0
Min, Max	2, 30	1, 43	1, 43
Extent of Exposure, n (%)			
Any Exposure	26 (96.3)	128 (100.0)	154 (99.4)
>= 1 Week	23 (85.2)	124 (96.9)	147 (94.8)
>= 2 Weeks	18 (66.7)	113 (88.3)	131 (84.5)
>= 3 Weeks	14 (51.9)	55 (43.0)	69 (44.5)
>= 4 Weeks	11 (40.7)	43 (33.6)	54 (34.8)
Dose Changes, n (%)			
Any Up-Titration	4 (14.8)	21 (16.4)	25 (16.1)
Any Down-Titration	5 (18.5)	45 (35.2)	50 (32.3)

(Source: Derived from Study OTR3001's report, Table 12.1.4.1, page 209).

While the mean oxycodone dose was 30 mg per day, the ranges show that some of the older patients required a much larger daily dose, as much as 160 mg per day.

Pain scores were recorded, but as an open-label study without a comparator, the efficacy data cannot be used to support a finding of efficacy. The study was intended to provide safety data and pharmacokinetic data. Details of the study design, conduct, and results can be found in Dr. Muniz' review.

Twenty three patients continued to receive OxyContin in the extension study, OTR 3002. The range of daily doses was from 20 mg to 56 mg per day and 13 of the twenty three patients continued on OxyContin for at least 28 weeks.

Study OC96-0602 was intended to be a study to evaluate the conversion of patients, ages 6 to 12 years, from immediate-release oxycodone to OxyContin. Only 13 patients of the planned 100 were enrolled before the study was discontinued for administrative reasons.

OTR1020 was an open-label study to characterize the PK and safety of single-dose and multiple-dose reformulated OxyContin tablets in pediatric inpatients aged 6 to 16 years. Safety and full pharmacokinetic data available from 30 patients, five in the 6 to < 12 age group and 25 in the ≥ 12 to ≤ 16 age group. Two patients discontinued early due to loss of vascular access and unwillingness to have additional access. Eighteen patients received a single dose of study drug and seven patients received five doses (maximum number allowed on study). The mean daily dose of study drug was 30 mg and 25 mg in the older age group and younger age groups, respectively. Most of the patients used supplemental pain medications.

Safety – Deaths

There were four deaths in the safety database. These all occurred in Study OTR3001 and none appear to be attributable to study drug. One patient was a 7 year old with Stage 4 neuroblastoma. The patient was titrated from OxyContin 15 mg twice daily to 15 mg in the morning and 10 mg in the evening for somnolence on Study Day 2, but On Day 3 was reported to have worsened edema and was treated with dexamethasone. On Day 5 the patient presented with headache and oliguria and she progressed with breathing irregularity, coma, and convulsion, prior to death. The investigator considered these serious adverse events to be the result of progression of the patient's malignancy.

A 15 year old patient with metastatic rhabdomyosarcoma was started on OxyContin 15 mg twice daily and titrated to 15 mg in the morning and 20 mg in the evening on Study Day 3, with further adjustment up and down on Days 7 and 8. On Study Day 18, the patient was hypoxic and comatose and later died. The investigator considered these serious adverse events to be the result of progression of the patient's malignancy.

A 10 year old with a history of neuroblastoma was admitted for management of lower body swelling and was started on OxyContin 10 mg twice daily for pain, titrated to 20 mg twice daily on Day 2. On Day 4 the patient's parents requested discontinuation of OxyContin and initiation of IV morphine for pain control. The patient died later that day. The investigator considered the patient's death to be unrelated to study drug.

A 16 year old with a history of ovarian tumor, bone marrow transplant, parasagittal mass with hemiparesis and seizures was started on OxyContin 60 mg. Her parents withdrew her from the study after one dose due to inadequate analgesic effect. The patient died 25 days later following a series of hospitalizations for cancer-related complications.

Safety – Serious Adverse Events

Serious adverse events were reviewed as a combined dataset from Studies OXP3003, OTR3001, and OXP1005, and individually for the remaining studies. These have been reviewed in detail by Dr. Muniz (starting page 110). This memo will focus on the serious adverse events from Studies OTR3001 and OTR3002 because the focus of this supplemental application is the use of OxyContin in pediatric patients.

The following two patients experienced serious adverse events for which a contribution by OxyContin cannot be ruled out. However, the assessment of relatedness appears weak given the symptoms being consistent with the recent surgery for the first patient, and occurring following a slow taper over 16 days for the second patient.

A 16 year old with a history of acoustic neuroma removal presented with diplopia, intermittent vomiting, vertigo, disequilibrium, dizziness, headache, and lethargy, three days after starting on OxyContin 10 mg twice daily, along with a history of no bowel movement for nine days. The symptoms resolved during hospitalization and the events were considered possibly related to the study drug by the investigator.

A 14 year old with a history of bilateral club feet, obesity, cardiac murmur, and orthopedic surgeries began treatment with OxyContin 30 mg twice daily reduced to 15 mg twice daily by Day 8, and 10 mg twice daily by Day 16. On Day 17, he was hospitalized due to multiple falls requiring surgical revision of an external fixator. The investigator considered the falls unrelated to study drug, although it is possible that there may have been some relationship to treatment with OxyContin.

The following 21 patients experienced multiple serious adverse events that do not appear attributable to study drug, but rather, reflect the complex nature of the underlying cancers and surgical histories.

1. A 13 year old who underwent a Nuss procedure to correct pectus excavatum deformity with thoracoscopy was started on OxyContin 20 mg twice daily, decreased to 10 mg twice daily on Day 8, because the patient's pain was well-controlled. On Study Day 8, the patient presented to the emergency room with increased chest and back pain and a fever of 100.8°F. Surgical assessment concluded there were no unexpected surgical complications with a persistent right apical pneumothorax, small bilateral pleural effusions, and subsegmental atelectasis at the left base. The surgical team requested a pain evaluation and the patient was prescribed continuation of morphine and ibuprofen as needed, and an increase of OxyContin to 20 mg in the morning and 10 mg at night. The patient completed 15 days on OxyContin and the event was attributed to the surgical procedure.

2. A 16 year old with a history of non-metastatic left tibial osteosarcoma and various orthopedic reconstructive surgeries, presented with chemotherapy-induced neutropenic fever four days after completing four weeks of treatment with OxyContin.
3. A 16 year old with a history of sickle cell disease, multiple vaso-occlusive episodes, splenectomy, and migraine headaches, developed a headache the day prior to starting OxyContin 40 mg twice daily for pain related to a vaso-occlusive crisis. She reported intermittent nausea and vomiting followed the next day by worsened headache with nausea, vomiting, photophobia, and decreased food intake. On Study Day 8, OxyContin was increased to 50 mg twice daily for worsened leg pain from the previous vaso-occlusive crisis. On Day 12 she was diagnosed with status migrainosus and was admitted to the hospital for treatment. The investigator assessed this as unlikely to be related to the study drug. She was treated with Norco for her leg pain, and IV and oral valproic acid for her migraine headache with positive results. She was discharged from the hospital on Day 13 and OxyContin was discontinued. The investigators decided to terminate the patient's participation from the study as the patient did not believe the study drug was helping with pain.
4. An 11 year old with a history of Ewing's sarcoma, chemotherapy-induced neutropenia, anemia, mouth/jaw pain, gait disturbance and episodes of upper extremity paresthesias was started on OxyContin 10 mg twice daily. On Study Day 9 the study drug was discontinued because the mother felt the patient's pain was improved and that he no longer needed the medication. On Day 14 the patient became neutropenic with back and mouth pain. On Day 17 he was hospitalized for febrile neutropenia.
5. A 10 year old with a history of osteosarcoma, liver and renal toxicity secondary to methotrexate, a history of radical tibial resection and allograft reconstruction, was started on OxyContin 40 mg twice daily. The investigator decided to wean her off OxyContin on Study Day 14 because her pain had improved, and she was off OxyContin as of Day 20. On Day 26, the patient presented with fever and neutropenia attributed to infection and mucositis secondary to chemotherapy.
6. A 14 year old with a history multiple injuries resulting from a 40-foot fall from a bridge requiring numerous vascular, orthopedic, and reconstructive surgeries was started on OxyContin 20 mg twice daily. Her last dose was Study Day 8. On Day 23 she was hospitalized with a diagnosis of osteomyelitis.
7. A 12 year old with a history of Ewing's sarcoma, ongoing chemotherapy, radiotherapy, right lower limb weakness, and spinal cord compression was started on OxyContin 20 mg twice daily. On Day 27 she presented with fever, hypotension and a mild headache. She was found to have an elevated white blood cell count, decreased hemoglobin and platelet count and was febrile.
8. A 12 y/o with a complex history including Hepatitis A and B, anemia, acute lymphoblastic leukemia, chemotherapy, renal failure, superior vena cava obstruction,

main bronchus compression, febrile neutropenia, abdominal and chest pain, pseudomonas sepsis, disseminated shingles, vincristine-related neuropathy, and epistaxis was started on OxyContin 20 mg twice daily. On Day 13, she presented with symptoms consistent with clostridial gastroenteritis and was found to be neutropenic. She was hospitalized intermittently for treatment of the infection, diarrhea and vomiting, and continued 27 days of study participation.

9. A 16 year old with a history of scoliosis and corrective surgery was started on OxyContin 20 mg twice daily that was decreased to 15 mg twice daily over two days. On Day 26, the patient presented with a change in posture of the spine/neck. He developed a rash after a contrast-enhanced CT scan. The patient completed 28 days on OxyContin. He was later found to have CT scan findings consistent with a post procedural complication was scheduled for corrective surgery.
10. A 16 year old with a history of Ewing's sarcoma, post-operative anemia, and constipation was started on OxyContin 10 mg in the morning and 15 mg in the evening. On Day 9, she was hospitalized with a fever, sore throat, rhinorrhea, vomiting, abdominal pain, tachycardia and hypotension. She was diagnosed with febrile neutropenia, influenza and vomiting. She completed 28 days on OxyContin while receiving treatment with antibiotics and further chemotherapy.
11. A 10 year old with a history of osteosarcoma and chemotherapy, was started on OxyContin 10 mg twice daily. On Study Day 9, the patient was hospitalized with neutropenic fever, and was diagnosed with a skin abscess. She completed 26 days of treatment with OxyContin.
12. A 14 year old with a history of sickle cell disease, multiple vaso-occlusive episodes, obesity, and insulin resistance was started on OxyContin 30 mg twice daily titrated to 40 mg twice daily. Her last dose of study drug was On Day 14. On Day 16 she presented with severe pain associated with her sickle cell disease.
13. A 16 year old with a history of Systemic Lupus Erythematosus, antiphospholipid syndrome, and multiple related complications requiring vascular surgical interventions was started on OxyContin 30 mg twice daily. On Study Day 5 he developed headaches with photophobia and phonophobia, and epistaxis while on anticoagulant therapy. Head CT showed complete opacification of the left frontal sinus and focal thickening of the left maxillary sinus. He completed 29 days of treatment with OxyContin. The patient was then diagnosed with an axillary vein thrombosis on Day 34, and gangrene of the toe on Day 37.
14. A 16 year old with a history of lumbar disk avulsion fracture, gait problems, bilateral leg pain, lumbar spinal stenosis, and lumbar radiculopathy, was started on OxyContin 40 mg twice daily reduced to 40 mg in the morning and 30 mg in the evening on Day 3. On Day 11 he complained of pain and agitation that was treated with diphenhydramine and haloperidol IM. On Day 22 he presented to the emergency room with acute exacerbation of back pain and OxyContin was discontinued. The next day he was hospitalized and

treated with hydromorphone. An MRI showed asymmetric edema within paraspinal soft tissues and he was treated with corticosteroid injections.

15. A 15 year old with a history of osteosarcoma, radical resection of right tibia six days prior to the start of the study, and periodic pancytopenia secondary to chemotherapy, was started on OxyContin 30 mg twice daily, titrated to 50 mg twice daily by Day 10. On Day 21, she started chemotherapy and the OxyContin was decreased to 40 mg twice daily on Day 27. On Day 30, she was hospitalized with neutropenic fever.
16. A 14 year old with a history of sickle cell disease with multiple vaso-occlusive episodes, stroke, obesity, iron overload secondary to repeated red blood cell transfusions, hypertension, and acquired immunodeficiency was started on OxyContin 20 mg in the morning and 10 mg in the evening, and decreased to 10 mg twice daily the next day. On Day 16, she began to experience worsening back pain, on Day 18, she was hospitalized with a fever and diagnosis of worsened vaso-occlusive pain crisis.
17. A 14 year old with a history of Ewing's sarcoma, thrombocytopenia, spinal cord compression, and adrenal hyperplasia was started on OxyContin 10 mg twice daily. On Day 15 chemotherapy was started and on Day 17 she took the last dose of the study drug. Chemotherapy was completed on Day 19 and on Day 21, she began experiencing SAEs of abdominal pain, diarrhea, and vomiting, considered related to chemotherapy.
18. A 14 year old with a history of stage IV neuroblastoma and related surgeries and complications received chemotherapy prior to starting the study. She was started on OxyContin 15 mg twice daily. On Day 2, she presented to the emergency room with neutropenia, pyrexia, and cellulitis at a right hip biopsy site. She completed 29 days of treatment with OxyContin.
19. A 13 year old with a history of osteochondrosis and spinal fusion surgery was started on OxyContin 20 mg twice daily. On Day 10, an SAE of back wound seroma was reported and he was hospitalized for irrigation and excisional debridement. He completed 19 days of treatment with OxyContin.
20. A 15 year old with a history of spinal fusion surgery for scoliosis immediately preceding the study was started on OxyContin 20 mg twice daily. On Day 7, she was diagnosed with a draining seroma on her back, related to her back surgery. She completed the study on Day 16.
21. A 15 year old with a history of pancreatitis 11 years prior to the study and recent spinal fusion surgery for scoliosis was started on OxyContin 10 mg twice daily and on a follow up visit on Day 5, complained of abdominal pain, constipation, and back wound discharge. Work up revealed an increasing amylase level and she was admitted on Day 9 for further evaluation of abdominal pain and elevated pancreatic enzymes. The next day the SAE was considered resolved, she was discharged from the hospital, and she subsequently completed the study on Day 18. Dr. Feeney considers this event possibly

related top study drug, but the resolution prior to discontinuation of study drug makes this unlikely.

There were five patients with serious adverse events in the continuation study, OTR3002. Aside from one patient with a serious adverse event of constipation, the following four patients had serious adverse events that are not attributable to study drug.

A 12 year old with a history of acute lymphoblastic leukemia, spinal compression fracture, helicobacter pylori infection, and intervertebral disc disorder who completed four weeks of OxyContin 30 mg twice daily in Study OTR3001 continued into OTR3002 on OxyContin 20 mg twice daily. On Day 5, she was hospitalized with worsening vomiting, headache, and back pain all attributed to her leukemia). She completed the study on OxyContin 20 mg twice daily.

A 14 year old with a history of sickle cell anemia with multiple vaso-occlusive crises, Raynaud's phenomenon, completed OTR3001 on OxyContin 10 mg twice daily and was enrolled in OTR3002. During the course of the next five months, this patient had a total of four vaso-occlusive episodes with multiple admissions, obviously attributed to her sickle cell disease and not to the study drug. The study drug was interrupted at least one while she received IV morphine. During this time, the OxyContin dose fluctuated between 10 mg twice daily, 15 mg twice daily, 15 mg in the morning and 20 mg in the evening. She completed the study at a 10 mg twice daily dose.

An 11 year old with a history of optic nerve glioma, headaches, anemia, and back pain from chemotherapy completed the OTR3001 on OxyContin 10 mg twice daily, which she continued when she was enrolled on OTR3002. A month later she received chemotherapy and was hospitalized with a fever. The patient was able to complete the study on OxyContin 10 mg twice daily.

An 11 year old with a history of sickle cell anemia with multiple vaso-occlusive episodes, seizures, constipation, and sleep apnea completed OTR3001 on OxyContin 10 mg twice daily and was enrolled on OTR3002 on the same dose. On Day 18, she complained that she could not fully move her legs due to severe pain and she was admitted to the hospital with an SAE of vaso-occlusive crisis. While she was hospitalized she continued on the study drug.

Adverse Events Leading to Discontinuation and Treatment Emergent Adverse Events.

In Study OTR3001 events leading to study discontinuation and treatment emergent nonserious adverse events were consistent with known opioid-related adverse events, as shown in the following table from Dr. Muniz' review (page 128). Events of note include hypoxia leading to study discontinuation, as well as euphoria, lethargy, and convulsion, each in one patient.

Table 34. Incidence of TEAEs Leading to Study Drug Discontinuation by SOC and Preferred Term. Study OTR3001

System Organ Class (SOC) Preferred Term	Age Group		Total (N=155) n (%)
	6 to <12 Years (N=27)	≥12 to ≥16 Years (N=128)	
	n (%)	n (%)	
Any TEAEs Leading to Study Discontinuation	3 (11.1)	7 (5.5)	10 (6.5)
Ear and labyrinth disorders	0	1 (0.8)	1 (0.6)
Vertigo	0	1 (0.8)	1 (0.6)
Eye disorders	0	1 (0.8)	1 (0.6)
Diplopia	0	1 (0.8)	1 (0.6)
Gastrointestinal disorders	0	1 (0.8)	1 (0.6)
Vomiting	0	1 (0.8)	1 (0.6)
General disorders and administration site conditions	1 (3.7)	1 (0.8)	2 (1.3)
Irritability	1 (3.7)	0	1 (0.6)
Pain	0	1 (0.8)	1 (0.6)
Nervous system disorders	1 (3.7)	3 (2.3)	4 (2.6)
Headache	1 (3.7)	2 (1.6)	3 (1.9)
Coma	1 (3.7)	1 (0.8)	2 (1.3)
Dizziness	0	2 (1.6)	2 (1.3)
Balance disorder	0	1 (0.8)	1 (0.6)
Convulsion	1 (3.7)	0	1 (0.6)
Lethargy	0	1 (0.8)	1 (0.6)
Psychiatric disorders	1 (3.7)	1 (0.8)	2 (1.3)
Abnormal dreams	1 (3.7)	0	1 (0.6)
Euphoric mood	0	1 (0.8)	1 (0.6)
Renal and urinary disorders	1 (3.7)	1 (0.8)	2 (1.3)
Oliguria	1 (3.7)	0	1 (0.6)
Urinary retention	0	1 (0.8)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	1 (3.7)	1 (0.8)	2 (1.3)
Hypoxia	0	1 (0.8)	1 (0.6)
Respiratory disorder	1 (3.7)	0	1 (0.6)
Skin and subcutaneous tissue disorders	1 (3.7)	3 (2.3)	4 (2.6)
Hyperhidrosis	0	1 (0.8)	1 (0.6)
Pruritus	0	1 (0.8)	1 (0.6)
Rash pruritic	1 (3.7)	0	1 (0.6)
Urticaria	0	1 (0.8)	1 (0.6)

(Source: Study OTR3001's report, Table 34, page 122)

Note: Patients who experienced 2 or more adverse events within the same SOC or preferred term were counted only once.

N = number of patients in population groups and total.

n = number of patients with data.

Percentages are based on N.

As noted by Dr. Muniz, the most frequently reported treatment emergent adverse events occurring in at least 5% of patients in the safety population were vomiting (22%), nausea (15%), headache (14%), pyrexia (12%), and constipation (10%), diarrhea (5%), dizziness (8%) and pruritus (7%).

Dr. Muniz fully reviewed the laboratory data and vital signs. In the patient population enrolled, it is very difficult to associate the changes in lab values and vital signs with study drug, rather than underlying illness or concomitant treatment.

Looking across the safety database, it was noted that there were two patients (an 11 year old female and a 15 year old female) with treatment-emergent clinically significant oxygen desaturations in Study OTR3001. Additionally, there were four patients in the total population

(two each in the 6-11 age group and 12-17 age group) that experienced the treatment-emergent adverse event of “oxygen saturation decreased.”

Studies with Oxycodone Oral Solution

The safety profile of oxycodone oral solution has been fully reviewed by Drs. Muniz and Feeney. The adverse events were consistent with the known adverse events of opioids in this population. There were cases of apnea (in a newborn), hypoxia, and somnolence.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. The Applicant conducted studies requested in a pediatric written request. While the written request was not fulfilled completely due to under-representation of pediatric patients treated with OxyContin in the 6 up to 11 age range, the available data for patients 11 and older and from the studies of oxycodone oral solution were interpretable and did not demonstrate any unusual or unexpected safety findings.

10. Pediatrics

The application was reviewed at a meeting of the Pediatric Research Committee on May 13, 2015. The minutes from that meeting are reproduced below:

OxyContin (b) (4) WR Review

- Indication studied: Treatment of acute moderate to severe pain
- The Division provided a summary of the data included in the application. Importantly, the Division does not agree that the sponsor has fairly met the terms of the WR because the sponsor failed to enroll sufficient numbers of patients 6-11 years of age in the OxyContin study (study 3 of the WR; a clinical trial of extended-release oxycodone in pediatric patients with chronic pain). The Division noted that only 14 patients 6 to 11 years of age (approximately 10%) were enrolled compared to 141 patients 12 to 17 years of age. Thus, the Division's current plan is to limit the approval of the indication to chronic pain in pediatric patients greater than 12 years of age.
- The Division also noted that PK data were obtained in studies 1 & 2 of the WR in patients 1-17 years of age for the immediate release oxycodone product. (b) (4)

(b) (4) The Division questioned whether this PK information should be placed in the labeling for OxyContin. The PeRC recommended that this information **NOT** be placed in OxyContin labeling because it may lead the false assumption that these data relate to OxyContin rather than to the immediate release form of oxycodone. However, because this information is of public health benefit the PeRC recommended that a (b) (5)

- *PeRC Recommendations:*
- The PeRC agreed with the Division's assessment.

The Applicant requested pediatric exclusivity for OxyContin as a result of submission of these studies in response to a pediatric written request. (b) (4)

[Redacted]

[Redacted] (b) (4)

[Redacted] (b) (5), (b) (4)

It is unclear that a 5 mg tablet would result in the enrollment of a sufficient number of patients under the age of 11 to assess safety. The Applicant made a substantial attempt to enroll these younger patients. In the studies of oxycodone oral solution, there were patients that tolerated the 0.2 mg/kg dose of oxycodone which could easily translate into a total daily oxycodone dose of 20 mg given the range of weights for pediatric patients in the 6 to 11 year age range, suggesting the that the difficulty with enrollment in Study 3001 was not primarily limitations due to the lack of the 5 mg strength tablet.

11. Other Relevant Regulatory Issues

Inspections

Dr. Lee of the Office of Scientific Investigation identified an issue bearing on the integrity of the PK samples collected throughout Studies 1 and 2.

As summarized by Dr. Feeney and reproduced below (pages 8 and 9):

Dr. Hammer at the Stanford site was an investigator in both Studies 1 and 2. The Form FDA 483 for his site noted that, "The temperature log for the freezer did not include temperature records for the first nine of the total 15 months of PK blood sample storage." Dr. Lee commented, "The inadequate freezer temperature log may indicate more than inadequate recordkeeping and may include inadequate PK blood sample handling and storage for much of the study period (nine of 15 months). A comparison of the PK data from this CI site with those from other CI sites may be helpful in evaluating the reliability of the PK data from this CI site." The comments apply to Dr. Hammer's involvement in both Studies 1 and 2. Twenty-six patients birth - 4 years were enrolled in Study 1 at his site, while an additional 26 patients 5-16 years were enrolled in Study 2 at his site.

While it remains a possibility that this deficiency only represents a recordkeeping error, a failure to record the temperature at the stated times, Dr. Nallani has attempted to reconcile the finding in his Clinical Pharmacology review as follows:

- a) Document the long-term stability of the quality control (QC) solutions from the bioanalytical report;
- b) Document the stability of QC solutions over the fifteen freeze/thaw cycles available from the bioavailability report;
- c) He compared PK data from Study OXP3003 to another study, OXP3001.

Comparable clearance values are available from both studies for 5-16 year-old patients, suggesting that the data collected in OXP3003 were valid. By extrapolation, the comparability of the PK data across these two studies for patients in the 5-16 year age group would suggest that the PK data collected in Study OXP1005 from younger patients were also valid.

I agree that the comparable PK data across Studies OXP3003 and OXP3001 support the validity of the PK samples collected at the Stanford site for both Studies OXP3003 and OXP1005. I believe it is most likely that the lack of temperature data for the first nine months was a recordkeeping error. As such, the stability data provided by Dr. Nallani are reassuring for any short-term temperature variations that might have occurred. However, the stability of the analytes at ambient temperatures for long periods of time would be questionable. Further investigation and discussion with the Sponsor about this issue will be needed moving forward. For instance, if there were control samples stored concurrently with the patient samples in the Stanford refrigerator, the stability of those controls would provide additional evidence bearing on the validity of the patient samples.

It is important to resolve this prior to any [REDACTED]

(b) (5)

As the data are not currently intended for use to provide dosing information for an immediate-release product in the age range of 0 to 4 years, I concur with the conclusions of Drs. Feeney, Nallani, and Lee that the data from the Stanford site can be relied upon for this supplemental application and to support the proposed changes to the OxyContin labeling.

REMS

OxyContin is a part of the Extended-Release and Long-Acting Opioid REMS (ERLA REMS). The ERLA REMS has been reviewed by the team from DRISK and updated to reflect the new indication and associated information from the OxyContin labeling resulting from this supplemental application.

PMRs

Through review of the literature, the most recent Postmarketing Safety Update Report, and the clinical trial data submitted in support of this application, we have become aware of reports of unintentional overdose with opioids in children, reports of accidental injury, accidental exposure, and medication errors, and treatment-emergent clinically significant oxygen desaturations. Therefore, two postmarketing requirements have been included as part of this action, described in detail below.

There are no other unresolved relevant regulatory issues.

12. Labeling

The Applicant did not request a new indication. After review of the information provided in support of this supplemental application, it was determined that there were sufficient differences between the pediatric population studied and the adult population represented by the existing indication, to support adding a new indication to ensure this distinction was clearly evident to prescribers. Following a full assessment and physical examination, adults may be safely started on doses of OxyContin from 10 mg twice daily up to 40 mg twice daily, even if not previously receiving an opioid. Single doses greater than 40 mg or total daily doses greater than 80 mg are to be reserved for use in patients in whom tolerance to an opioid of comparable potency has been established. However, because the Applicant [REDACTED] (b) (4) and non-responsive

[REDACTED] OxyContin is indicated for use only in pediatric patients who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent as this is the population that was studied.

The new indication for OxyContin reflects this distinction as follows:

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 in:

- Adults; and
- 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 Dosage and Administration section of the labeling reflect the pediatric experience from Study OTR3001, and reflect the conversion factors used to switch patients from their prior opioid to OxyContin.

Relevant language is presented in Section 8.4, Use in Specific Populations, Pediatric Use, as follows:

The safety and efficacy of OXYCONTIN have been established in pediatric patients ages 11 to 16 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 16 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 [*see Dosage and Administration (2.1), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Trials (14)*].

Section 12.3 Clinical Pharmacology, Pediatric Use has the following new statement:

In the pediatric age group of 11 years of age and older, systemic exposure of oxycodone is expected to be similar to adults at any given dose of OXYCONTIN.

While the systemic exposure of oxycodone below the age of 11 appears to be greater than in older children, possibly due to decreased metabolic clearance in these patients with lower body weight, OxyContin is not labeled for use in this age group due to inadequate safety information. Therefore, this pharmacokinetic data were not included in the labeling.

Section 14, Clinical Studies, was updated with the following language.

OXYCONTIN has been evaluated in an open-label clinical trial of 155 opioid-tolerant pediatric patients with moderate to severe chronic pain. The mean duration of therapy was 20.7 days (range 1 to 43 days). The starting total daily doses ranged from 20 mg to 100 mg based on the patient's prior opioid dose. The mean daily dose was 33.30 mg (range 20 to 140 mg/day). In an extension study, 23 of the 155 patients were treated beyond four weeks, including 13 for 28 weeks. Too few patients less than 11 years were enrolled in the clinical trial to provide meaningful safety data in this age group.

Dr. Taylor of the Division Pediatric and Maternal Health provided labeling recommendations that were incorporated into the package insert.

Labeling recommendations for the package insert and medication guide from the patient labeling teams from the Office of Prescription Drug Promotion and the Division of Medical Policy Programs were incorporated into the package insert and medication guide.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval
- Risk Benefit Assessment

OxyContin has been used off-label to manage pain in pediatric patients. The studies conducted in support of this application provide important dosing, pharmacokinetic, and safety information that is useful for prescribers who treat pediatric patients with conditions that require opioid analgesics, and in particular, that require management of pain that cannot be adequately managed with nonopioid analgesics or immediate-release opioid analgesics. Acceptable safety has been demonstrated with the use of OxyContin in pediatric patients 11 years of age and older who were already receiving and tolerating a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

There is no expectation that this approval and addition of a pediatric indication should necessarily expand the use of OxyContin for pediatric patients. Of great importance is that this approval should not be interpreted to mean that prescribers can assume that it is safe to start prescribing OxyContin in the absence of a full understanding about the management of pediatric patients with pain requiring opioid analgesics, without the particular knowledge about all of the risks associated with OxyContin, and without knowledge how to appropriately select patients, determine the correct dose, and monitor patients once treatment with OxyContin has been initiated.

- Recommendation for Postmarketing Risk Management Activities

OxyContin is part of the ERLA REMS which has been updated to reflect the information from this new indication.

- Recommendation for other Postmarketing Study Commitments

Since OxyContin was approved on April 5, 2010, we have become aware of clinical trial results in opioid-tolerant pediatric patients primarily aged 11-17. During the trial, there were two patients (an 11 year old female and a 15 year old female) with treatment-emergent clinically significant oxygen desaturations. Additionally, there were four patients in the total population (two each in the 6-11 age group and 12-17 age group) that experienced the treatment-emergent adverse event of “oxygen saturation decreased.” We have also become aware of a study in the published literature describing the frequency of unintentional overdose with opioids in children covered by Tennessee Medicaid. In this study, designed to develop coding algorithms to identify serious opioid-related adverse events in pediatric patients, 25 of the 31 cases identified by the algorithm for unintentional overdose were confirmed by medical records ((positive predictive value of 81%).³ We have also become aware of reports of adverse events, accidental injury, accidental exposure, and medication errors, which are of particular concern for the pediatric population.⁴ We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of respiratory depression, accidental injury, overdose, misuse, accidental exposure, and medication errors in pediatric patients aged 17 years and younger.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

2923 – 1 To assess the serious risks of respiratory depression, accidental injury, overdose, misuse, accidental exposure, and medication errors associated with the use of OxyContin in opioid-tolerant pediatric patients aged 11-17, and to assess the serious risks of respiratory depression, accidental injury, overdose, misuse, accidental exposure, and medication errors associated with the use of the product in children who are either younger than the approved age range or who do not meet the labeled criteria for opioid tolerance, provide reports of all postmarket adverse events occurring in children aged 17 and younger related to respiratory depression, accidental injury, overdose, misuse, accidental exposure, and all medication errors, regardless of outcome. After three years of submitting reports, submit a comprehensive analysis of these adverse event and medication errors reports, and provide an explanation of how you have addressed them.

The timetable you submitted on July 13, 2015, states that you will conduct this reporting according to the following schedule:

Final Protocol Submission: 08/2015

Interim Report Submission: 12/2015

³ Chung CP, Callahan ST, Cooper WO, et al. Development of an algorithm to identify serious opioid toxicity in children. BMC Research Notes 2015; 8: 293.

⁴ NDA 22272, Periodic Safety Update Report, June 9, 2015.

Interim Report Submission: 12/2016
Interim Report Submission: 12/2017
Interim Report Submission: 12/2018
Final Report Submission: 04/2019

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- Conduct a nationally representative drug utilization study of sufficient detail to characterize use of OxyContin in children aged 17 years and younger. The data from this study will provide a denominator for the risks assessed in PMR #2923-1 and any future safety studies and clinical trials used to assess those risks. The following analyses should be conducted with the data collected:
- 1) Total number of prescriptions dispensed across all settings of care
 - a. stratify by age group (0-1, 2-5, 6-10, 11-17), indication, setting of care, and prescriber specialty, and geographic location
 - b. provide characteristics of dose dispensed (mean, median, range)
 - 2) Total number of unique patients receiving dispensed prescriptions across all settings of care
 - a. stratify by age group (0-1, 2-5, 6-10, 11-17), indication, setting of care, and prescriber specialty
 - i. provide unique incident users every quarter-year
 - b. patient demographics of users of the product
 - c. clinical characteristics of users of the product (including what percentage of patients are opioid tolerant at the time they get the OxyContin prescription)
 - 3) Duration of therapy (include definitions of allowable gaps in drug therapy in calculating duration of therapy)
 - a. total and stratified by indication
 - b. exploration of possible 'intermittent' use
 - c. percentage of patients switching from immediate-release opioids to OxyContin
 - d. percentage of patients switching from other extended-release opioids to OxyContin
 - e. dose adjustments over time

The timetable you submitted on July 13, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 10/2015
Interim Report Submission: 01/2016
Interim Report Submission: 12/2016
Interim Report Submission: 12/2017
Final Report Submission: 12/2018

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARON H HERTZ
08/13/2015