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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: • 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.
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> 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 ≤ 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 ≤ 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.

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