CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
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Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

POST-MARKETING OBSERVATIONAL STUDIES

NDA #:	22-272
Drug Name:	OxyContin (oxycodone hydrochloride)
Indication(s):	Management of moderate to severe pain
Applicant:	Purdue Pharma L.P.
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1 EXECUTIVE SUMMARY

OxyContin (OC) was first approved by the Agency on December 12, 1995. OxyContin is a schedule II controlled substance with label indication, "For the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days." Oxycodone products are common targets for both drug abusers and drug addicts. The Agency approved the new reformulated OxyContin (ORF) in April 5, 2010. The new formulation of OxyContin was designed to make breaking, dissolving, crushing or chewing the tablet more difficult. Purdue ceased shipping the original formulation of OxyContin on August 5, 2010 and began shipping only reformulated tablets from August 9, 2010. As of January 2011, more than (b) (4) of filled prescriptions for OxyContin were reformulated OxyContin. At the Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on October 21 and 22, 2010, Purdue proposed multiple post-marketing studies to assess the effects of reformulated OxyContin in the setting that reflects the actual usage. Purdue submitted preliminary reports on the studies as May 2012 to the Agency on July 31, 2012.

The Division of Epidemiology II requested the Division of Biometrics VII to review the preliminary report submitted in July 2012. This review provides a statistical evaluation of the design, methods and proposed analyses for studies 1, 2 and 6. An assessment of the preliminary results is also provided. However, a thorough and complete evaluation of the study results should be conducted upon the completion of the studies. A separate biostatistical review by Dr. Zhang addresses studies 3, 4, 5, and 11.

Study 1 was designed to investigate the routes and rates of OxyContin abuse among patients in substance abuse treatment programs in the ASI-MV Connect NAVIPPRO System. Specifically, patterns of past 30-day abuse of reformulated OxyContin (ORF) are compared to those of the original formulation (OC) after the introduction of ORF. In addition, the study assessed abuse through routes of administration (ROA) that require tampering, particularly snorting, injecting, and smoking. These were compared to original OxyContin and comparator opioids. The report covers preliminary analyses of the data from June, 1, 2009 to March, 31, 2012.

Generalized linear mixed model was used to estimate pre-ORF and post-ORF period percentages and relative percent change from the pre to post ORF period. Specifically, quarterly prevalence of past 30-day abuse for OC and ORF were compared to changes in comparator opioid analgesics ER morphine and ER oxymorphone. Although the data presented for 6 quarters post ORF is consistent with the study hypotheses of lower rates of abuse ORF, its profile compared to OC beyond the second quarter is very similar. The preliminary results show a considerable drop in levels of abuse through both oral and non-oral (smoking , snorting and injecting) after the introduction of ORF; however, with limited data points, the results do not support any substantial long term pattern.

Study 2 investigated the changes in rates of opioid overdose and poisoning (OOP) among patients dispensed OxyContin or comparator opioids in the Kaiser Permanente Northwest and Northern California regional health care systems before and after the introduction of

reformulated OxyContin (ORF). The study used chart abstraction data from February 2003 to July 2010, and 15 months following the introduction of ORF. The rates of OOP event associated with OxyContin use were compared to three groups of comparator opioids: a) other extended release opioids, b) immediate release, single entity oxycodone, and c) all other prescription opioids.

The findings at the time of this report do not suggest any substantial changes in dispense patterns or abuse rates or both. Data were only available for one full six-month period following the transition from the OC to ORF at this point. Limited data in the post-ORF period precludes the adequate assessment of the study results.

Study 6 used data from the Ohio Prescription Monitoring Program (PMP) and IMS LRx prescription database. The PMP study examined the number of individuals who obtained prescriptions by multiple prescribers and filled at multiple pharmacies. In the IMS LRx analysis, the goal was to assess the potential changes in the proportion of opioid shopping behavior among OxyContin users after the introduction of ORF. Doctor shopping was defined as a patient that visits multiple prescribers and pharmacies to obtain and fill more than necessary opioid prescriptions, in order to abuse or sell the excess opioids.

The PMP analysis consisted of data from August 8, 2008 to June 11, 2011. The IMS LRx analysis consisted of 2 six-month pre-periods (July to December 2009 and January to June 2010) and 2 six-month post-periods (January to June 2011 and July to December 2011). The PMP analysis used data from the Ohio Automated Rx Reporting System (OARRS). The study estimated the counts and rates of individuals who filled OxyContin prescriptions from a combination of 1-5 or more prescribers and 1-5 or more pharmacies. In IMS LRx analysis, the study used a database that consisted of patient de-identified longitudinal prescription from a sample of IMS Health retail and mail order prescriptions universe. Relative change in proportions was used to assess the shopping behavior of OxyContin from pre-ORF to post-ORF.

There are a total of 5 data points in the PMP analysis and 4 in the IMS LRx analysis. With very few data points, the analysis does not provide sufficient information to identify or establish a trend.

The design aspects of post-marketing observational studies on abuse deterrence were discussed in the Joint Meeting of the Anesthetic and Life Support Advisory Committee and the Drug Safety and Risk Management Advisory Committee in October 2010. The trend approach and the requirement of a sufficient period of time to establish the pattern of abuse and to demonstrate sustainability were emphasized by the committee. In order to properly characterize the abuse pattern over time, we need to be confident that the trend is stable and well characterized, which may require longer observation periods and the ability to consider the autocorrelation structure and possibly periodicity or seasonal patterns in the data. The accuracy, in terms of bias and variability, of the outcome measure would also affect the necessary length of the observational period. The three studies covered in this review had approximately 1 to 1.5 years of data after ORF was introduced into the market, corresponding to 2 to 6 data points depending on the data source. The adequacy of data points/structure for these studies should be further evaluated upon

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