FDA Briefing Document

Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Meeting

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Postmarketing safety issues related to reformulated

Opana ER®

ADDENDUM

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

Addendum to Background Package

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Subject:	Review of newly available epidemiologic data from the RADARS® Treatment Center Program
Drug Name(s):	Opana® ER (oxymorphone hydrochloride)
Application Type/Number:	NDA 201655
Applicant/sponsor:	Endo Pharmaceuticals

Background:

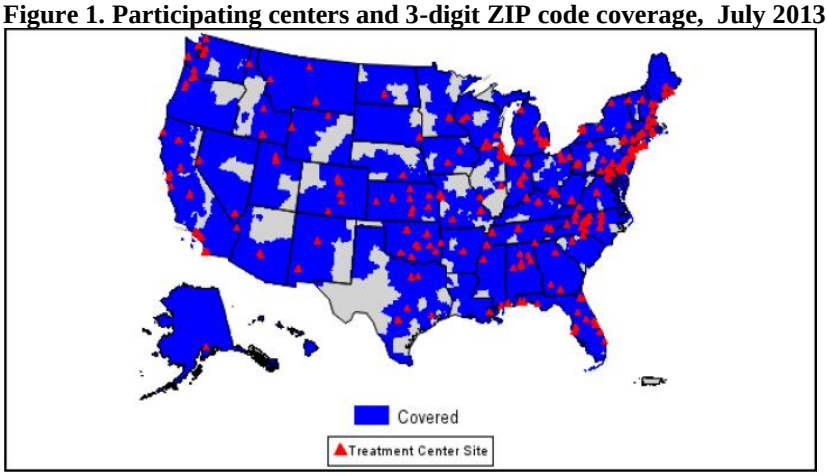
Considering the uncertainties remaining in the available postmarketing data, FDA sought additional sources of information that might help to inform the overall discussion of the risk-benefit balance of Opana extended-release (ER) relative to other oxymorphone products. In particular, there was interest in data that might provide clarity on the relative abuse rates for reformulated Opana ER and generic oxymorphone ER, given the inconsistent findings in the NAVIPPRO® and RADARS® Poison Center Studies, which were discussed in our original review. Also, given the geographic heterogeneity of abuse patterns observed in these studies, there was also interest in examining abuse of these products in a study population with a different geographic distribution.

FDA recently awarded contracts to obtain direct access to data from individuals entering or being assessed for substance abuse treatment. One of the data resources included in these contracts is the Researched Abuse, Diversion and Addiction-Related Surveillance System (RADARS®) Treatment Center Program, maintained by the Rocky Mountain Poison and Drug Center. FDA commissioned the following report, analyzing these data: **"Drug Specific Report—Route of Abuse Patterns for Opana Extended Release and Selected Comparator Opioids among Individuals Entering Treatment for Opioid Addiction: RADARS® System Report,"** received by FDA on February 17, 2017. The purpose of this addendum to the March 13-14 Advisory Committee meeting background package is to provide a brief summary and discussion of the key findings of this report. Unless otherwise noted, all tables and figures are abstracted directly from the report.

Methods

The RADARS® Treatment Center Program surveys individuals entering treatment for opioid use disorder, asking them to identify specific products they have abused in the past. The surveillance network includes both federally funded medication-assisted treatment programs (the Opioid Treatment Program, or OTP) and other, predominantly private treatment programs (the Survey of Key Informants' Patients, or SKIP). It has a different coverage area than the NAVIPPRO® ASI-MV® surveillance system, but like NAVIPPRO®, employs a convenience sample of sites that changes over time. In 2009, there were 115 participating sites in 48 states, and in 2015, there were 200 sites in 49 states. Figure 1 shows the coverage area for the time period July 2013 through June 2016.

Figure 1. Participating centers and 3-digit ZIP code coverage, July 2013 – June 2016



The RADARS Treatment Center Survey asks respondents about drugs used in the past month to get high, which is defined as "abuse." In 2Q 2011, the survey also began asking respondents if they had injected the drug in the past month, and in 3Q 2015, the program began asking about other routes of administration, including chewing, smoking, and snorting. The survey is organized into section by each opioid molecule, with subsections for specific formulations and products. The survey is updated regularly to add new products entering the market. An oxymorphone section containing selections for Opana (IR), Opana ER, and other (generic) oxymorphone products was added in 2Q 2011. Figure 2 below shows the section of the survey where respondents are asked about past-month abuse of oxymorphone products. Note that Opana (IR) is the first oxymorphone product listed.

Figure 2. Oxymorphone section of RADARS® Treatment Center survey (SKIP Version 18, 10/1/2013)

OXYMORPHONE Used to get high	Used in past month to get high	Injected in past month
FORMULATION UNKNOWN		
Oxymorphone, type unknown	☐	☐
TABLETS – IMMEDIATE RELEASE (IR)		
Opana® tablets	☐	☐
Oxymorphone IR tablets, not listed above	☐	☐
Oxymorphone IR tablets, not sure of name	☐	☐
TABLETS – EXTENDED RELEASE (ER)		
Opana ER® tablets	☐	☐
Oxymorphone ER tablets, not listed above	☐	☐
Oxymorphone ER tablets, not sure of name	☐	☐

Source: Provided by the Rocky Mountain Poison and Drug Center, included with permission

Multiple analyses were requested, examining abuse and routes of abuse reported for Opana ER and the following comparators: Opana immediate-release (IR), generic ER oxymorphone, generic IR oxymorphone, ER morphine, ER oxycodone, ER hydromorphone, and IR oxycodone. IR oxycodone represents both single-ingredient and combination products. Analyses were conducted for Opana ER and each comparator to calculate the following:

1. **Abuse prevalence**: Number of mentions for a drug per 100 surveys that contained the specific drug being analyzed
2. **Utilization-adjusted rates**: Number of mentions for a drug per 100,000 dosage units dispensed within the ZIP code coverage for returned surveys that contained the specific drug being analyzed
3. **Percent of respondents reporting abuse of each drug who indicated abusing it via a specific route**.

The requested time periods for these analyses were as follows:

1. 1Q 2009 – 2Q 2010 (pre-period, prior to OxyContin reformulation)
2. 1Q 2011 – 4Q 2011 (pre-period, after introduction of reformulated OxyContin and two-quarter transition period, up to introduction of reformulated Opana ER)
3. 3Q 2013 – 2Q 2016 (post-period, after Opana ER reformulation and six-quarter transition period)

Key Findings

The total number of surveys included in the overall analytic sample was 12,043 in the first time period, 10,256 in the second time period, and 26,996 in the third time period. However, the number of surveys included in analyses for each drug varied, depending on when specific drugs were added to the survey, as shown in Table 1, as oxymorphone and hydromorphone products were added to the survey during the second study period.

Table 1. Total number of surveys returned containing each drug question, by study period

Drug Group	2009Q1-2010Q2	2011Q1-2011Q4	2013Q3-2016Q2
Opana® ER		7,266	26,996
Generic ER oxymorphone		7,266	26,996
Opana®		7,266	26,996
Generic IR oxymorphone		7,266	26,996
ER morphine	12,043	10,256	26,996
ER oxycodone	12,043	10,256	26,996
ER hydromorphone		9,617	26,996
IR oxycodone	12,043	10,256	26,996

Table 2 shows the number and percent of respondents reporting abuse of Opana ER and comparators (abuse prevalence). Overall, IR and ER oxycodone had the highest abuse prevalence. Of note was that, of the oxymorphone product groups, Opana (IR) had the highest abuse prevalence. Comparing the second to the third time periods, abuse prevalence declined for Opana ER, Opana (IR), ER morphine, and ER oxycodone. The prevalence of generic ER oxymorphone, generic IR oxymorphone, IR oxycodone, and ER hydromorphone abuse changed minimally. Of note, only the 7.5mg and 15mg dosage forms of generic oxymorphone ER were available during the 2011Q1-2011Q4 time period.

Of note, the proportion of completed surveys from Tennessee changed minimally across the three time periods, and particularly from the second to third time period. In the first time period 3.9% of surveys were from Tennessee, and 2.3% and 2.6% of surveys were from Tennessee in the second and third time period, respectively.

Table 2. Number and percent of respondents endorsing past month abuse, by drug group and study period.

Drug Group	2009Q1-2010Q2	2011Q1-2011Q4	2013Q3-2016Q2
Opana® ER		349 (4.8%)	1042 (3.9%)
Generic ER oxymorphone		123 (1.7%)	386 (1.4%)
Opana®		682 (9.4%)	1741 (6.4%)
Generic IR oxymorphone		151 (2.1%)	517 (1.9%)
ER morphine	1266 (10.5%)	1027 (10.0%)	1828 (6.8%)
ER oxycodone	4700 (39.0%)	3181 (31.0%)	4363 (16.2%)
ER hydromorphone		144 (1.5%)	423 (1.6%)
IR oxycodone	3230 (26.8%)	2093 (20.4%)	6579 (24.4%)

Table 3 displays the utilization-adjusted abuse rates for Opana ER and comparators. The most striking finding here is the extremely high rate for Opana (IR) relative to the other opioids, particularly during the third time period, with a rate more than 100 times that of Opana ER, generic ER oxymorphone, or generic IR oxymorphone.

Table 3. Rates of past month abuse per 100,000 dosage units dispensed, by drug group and study period

Drug Group	2009Q1-2010Q2	2011Q1-2011Q4	2013Q3-2016Q2
Opana® ER		1.061 (0.952, 1.178)	1.501 (1.412, 1.595)
Generic ER oxymorphone		61.386 (51.018, 73.242)	0.803 (0.724, 0.887)
Opana®		32.397 (30.011, 34.923)	210.106 (200.351, 220.212)
Generic IR oxymorphone		2.058 (1.743, 2.414)	1.307 (1.197, 1.425)
ER morphine	0.519 (0.491, 0.548)	0.489 (0.460, 0.520)	0.237 (0.226, 0.248)
ER oxycodone	1.160 (1.128, 1.194)	1.532 (1.479, 1.586)	0.855 (0.829, 0.880)
ER hydromorphone		7.330 (6.182, 8.630)	3.199 (2.901, 3.518)
IR oxycodone	0.139 (0.134, 0.144)	0.095 (0.091, 0.099)	0.097 (0.095, 0.100)

Table 4 displays the percent of respondents who reported abuse of each drug via the injection route, comparing the three quarter-period before Opana ER's reformulation to the three-year post-reformulation period, indicating that the percent of survey respondents reporting injection

abuse of Opana ER approximately doubled following the drug's reformulation. Again, the prevalence of injection abuse was higher for Opana (IR) than for Opana ER, with a lower percent reporting generic oxymorphone product injection. The percent of respondents reporting injection abuse of IR oxycodone also increased sharply, while the percent reporting ER oxycodone injection declined and the others remained relatively stable.

Table 4. Number and percent of respondents endorsing past month abuse via the injection route, by drug group and study period.

Drug Group	2011Q2-2011Q4	2013Q3-2016Q2
Opana® ER	60 (0.8%)	397 (1.5%)
Generic ER oxymorphone	36 (0.5%)	160 (0.6%)
Opana®	141 (1.9%)	603 (2.2%)
Generic IR oxymorphone	50 (0.7%)	225 (0.8%)
ER morphine	206 (2.8%)	625 (2.3%)
ER oxycodone	454 (6.2%)	814 (3.0%)
ER hydromorphone	52 (0.7%)	188 (0.7%)
IR oxycodone	106 (1.5%)	1223 (4.5%)

Table 5 depicts utilization-adjusted injection abuse rates for Opana ER and comparators for the same two time periods. These findings indicate that, adjusting for utilization, Opana ER injection abuse rates tripled after the product's reformulation. Again, rates for Opana (IR) were exceptionally high, particularly during the post-period, and increased more than 10-fold from the first to second time period. Utilization-adjusted injection abuse rates declined for all the other drug groups except IR oxycodone.

Table 5. Rates of past month abuse by injection, per 100,000 dosage units dispensed, by drug group and study period

Drug Group	2011Q2-2011Q4	2013Q3-2016Q2
Opana® ER	0.182 (0.139, 0.235)	0.572 (0.517, 0.631)
Generic ER oxymorphone	17.967 (12.584, 24.873)	0.333 (0.283, 0.388)
Opana®	6.698 (5.638, 7.899)	72.771 (67.078, 78.818)
Generic IR oxymorphone	0.682 (0.506, 0.899)	0.569 (0.497, 0.648)
ER morphine	0.133 (0.115, 0.152)	0.081 (0.075, 0.088)
ER oxycodone	0.304 (0.276, 0.333)	0.159 (0.149, 0.171)
ER hydromorphone	3.210 (2.398, 4.210)	1.422 (1.226, 1.640)
IR oxycodone	0.006 (0.005, 0.008)	0.018 (0.017, 0.019)

Table 6 shows the percent of those reporting past-month abuse of Opana ER and comparators who reported injecting each drug, before and after reformulation of Opana ER. The proportion of Opana ER abusers who reported injecting it more than doubled, from 17.2% to 38.1% across the time periods. Increases in injection were also seen among those reporting abuse of the other oxymorphone products, as well as among those abusing IR oxycodone, with a slight increase in the percent of ER hydromorphone abusers who reported injecting it. ER hydromorphone had the highest percent of abusers reporting injection of the drug.

Table 6. Number and percent of respondents indicating injection, among those indicating past-month abuse of the specified drug, by study period.

Drug Group	2011Q2-2011Q4	2013Q3-2016Q2
Opana® ER	60 (17.2%)	397 (38.1%)
Generic ER oxymorphone	36 (29.3%)	160 (41.5%)
Opana®	141 (20.7%)	603 (34.6%)
Generic IR oxymorphone	50 (33.1%)	225 (43.5%)
ER morphine	206 (34.6%)	625 (34.2%)
ER oxycodone	454 (23.5%)	814 (18.7%)
ER hydromorphone	52 (39.1%)	188 (44.4%)
IR oxycodone	106 (8.2%)	1223 (18.6%)

Finally, data on specific routes (in addition to injection) were available for Q3 2015 through Q2 2016. As shown in Table 7, injection was more commonly reported than snorting for Opana (IR), Opana ER, generic ER oxymorphone, ER morphine, and ER hydromorphone. Of note, in this population, only 22% of generic ER oxymorphone abusers reported snorting it, which was

similar to the percent for the other oxymorphone products. Snorting was more commonly reported than injection for both ER and IR oxycodone products.

Table 7. Number and percent of abusers of each drug who reported using via the nasal and injection routes, Q3 2015 – Q2 2016

	Total abuse reports (N)	Snorted N (%)	Injected N (%)
Opana ER	312	65 (20.8%)	138 (44.2%)
Generic ER oxymorphone	140	31 (22.1%)	58 (41.4%)
Opana	520	145 (27.9%)	199 (38.3%)
Generic IR oxymorphone	178	43 (24.2%)	79 (44.4%)
ER morphine	633	119 (18.8%)	199 (31.4%)
ER oxycodone	1278	359 (28.1%)	206 (16.1%)
ER hydromorphone	185	33 (17.8%)	71 (38.4%)
IR oxycodone	1934	701 (36.2%)	321 (16.6%)

Source: Table generated by reviewer, using data provided in "Drug Specific Report—Route of Abuse Patterns for Opana Extended Release and Selected Comparator Opioids among Individuals Entering Treatment for Opioid Addiction: RADARS® System Report"

Discussion

The most striking, and unexpected, finding from these analyses was the relatively high proportion of respondents who reported abusing Opana (IR), compared to Opana ER, which has a much higher prescription volume than Opana (IR). The high number of abuse mentions and very low utilization for Opana (IR) resulted in utilization-adjusted abuse rates that were more than 100 times higher than those for Opana ER. Neither the NAVIPPRO nor the RADARS Poison Center studies discussed in our original review suggested utilization-adjusted abuse rates for Opana (IR) that were higher than other oxymorphone products. It is important to note that Opana (IR) was the first product listed in the oxymorphone section of the RADARS Treatment Center Program survey, and that this survey does not use pill photographs to aid in the identification of specific products. OSE has observed that Opana ER is commonly referred to in the media simply as "Opana,"[1,2] and in internet drug discussion forums, Opana ER is sometimes referred to as "Opana" and generic ER oxymorphone as "generic Opana."[3] For these reasons, OSE finds that the exceptionally high abuse rates for Opana (IR) are not plausible, and are likely a result of substantial differential misclassification of other oxymorphone products, likely including Opana ER, as Opana (IR). Such misclassification would be expected to result not only in overestimation of Opana (IR) abuse rates but underestimation of abuse rates for Opana ER and possibly generic oxymorphone products.

The likelihood of misclassification among oxymorphone products limits the utility of these data; however, some of the findings are still of interest. First, there were a substantial number of generic ER oxymorphone, as well as generic IR oxymorphone, abuse mentions, although it is

[1] http://usatoday30.usatoday.com/news/nation/story/2012-07-10/opana-painkiller-addiction/56137086/1
[2] http://www.npr.org/sections/health-shots/2016/04/01/472538272/how-a-painkiller-designed-to-deter-abuse-helped-spark-an-hiv-outbreak
[3] https://www.reddit.com/r/opiates/comments/16ezkw/it_is_official_generic_opana_made_with_endos_old/

difficult to determine the actual abuse rates for the different oxymorphone products relative to one another, with any confidence. Nonetheless, the hundreds of generic ER oxymorphone mentions identified in this analysis further call into question the very small number of generic ER oxymorphone cases observed in the RADARS® Poison Center study discussed in our original review, and suggest that a substantial amount of abuse of these products is occurring.

Second, if one were to assume that most abuse mentions for Opana ER represent actual abuse of this product, then these analyses suggest a sharp increase in the percent of Opana ER abusers who inject the drug, as well as in the utilization-adjusted injection abuse rate for Opana ER following reformulation. These results are qualitatively consistent with the findings of the NAVIPPRO study in suggesting increases in injection abuse prevalence and utilization-adjusted rates for Opana ER after its reformulation. And they are consistent with the RADARS® Poison Center study discussed in our original review in suggesting increases in utilization-adjusted Opana ER injection rates after reformulation. Increasing injection use was, however, not unique to Opana ER abusers. There was also increased reporting of injection among those abusing Opana (IR) and generic oxymorphone products, although the relative increases were of smaller magnitude than for Opana ER. These increases are, again, difficult to interpret as some unknown proportion of Opana (IR) abuse mentions likely actually represent abuse of Opana ER and possibly abuse of generic oxymorphone products. The patterns seen in comparators in this study suggest a complex and changing landscape of opioid abuse patterns. ER oxycodone and ER morphine injection abuse decreased, while increases in IR oxycodone abuse, particularly via the injection route, increased. During this time period, a growing proportion of the oxycodone market was single-entity IR oxycodone,[4] which may be more likely than oxycodone/acetaminophen combination products to be abused via non-oral routes.

Interpreting changes in abuse rates and patterns over time is again complicated by the dynamic nature of the study sample, as changes in the geographic distribution and distribution of treatment program types may impact abuse patterns observed in the study sample. Because this is a much smaller sample than in the NAVIPPRO® study, using a restricted set of sites that contributed data in every quarter is not feasible, as it would have a severe negative impact on study power and generalizability. Of note, however, the proportion of completed surveys from Tennessee—which the NAVIPPRO study suggested has unusually high Opana ER abuse rates among those being assessed for substance abuse treatment—was relatively low and remained stable after Opana ER's reformulation.

The proportion of Opana ER abusers who reported injecting it during the post-period was lower than that seen in the NAVIPPRO study, a finding possibly related to differences in the geographical distribution of this study population and that covered in the NAVIPPRO study. Because data on routes other than injection were not collected by the RADARS Treatment Center Program until 2015, we could not assess changes in nasal abuse rates after Opana ER's reformulation. Findings on other routes, from the four quarters with available data, differed from the NAVIPPRO study in suggesting little difference in the routes reported among the different oxymorphone products; however, misclassification within this product group would be expected to attenuate differences in the observed routes for the products.

[4] Wong, Jennie et al. "ERLA REMS Drug Utilization Review, May 26, 2016." Entered into DARRTS June 8, 2016.

Conclusions

Suspected differential misclassification, particularly of Opana ER as Opana (IR), limits the interpretability of these results. However, if one were to assume that most mentions of Opana ER abuse do represent actual abuse of this product, then these findings are qualitatively consistent with the RADARS® and NAVIPPRO® studies discussed in our original review in indicating that following Opana ER's reformulation, (1) the proportion of Opana ER abusers who reported injecting it increased substantially, and (2) Opana ER injection abuse rates also increased. Interpreting changes in abuse rates and patterns over time using these data is again complicated by the dynamic nature of the study sample, and comparisons with other oxymorphone products was complicated by the aforementioned misclassification issues. Although the hundreds of generic ER oxymorphone abuse mentions suggests that a substantial amount of abuse of these products is occurring, the misclassification issues make it difficult to determine relative rates of abuse among the oxymorphone products.