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FDA Drug Safety and Risk Management and Anesthetic and Analgesic Drug Products Advisory Committees

Reformulated Opana ER: extended release oxymorphone and general discussion about abuse deterrence

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(I have no financial conflict of interest)

Estimated requirements of oxymorphone for 2016 (grams)

	Million grams	% of world needs
World	20.9	------
U.S.	12.0	57.4
Italy	3.5	16.7
Switzerland	2.5	12.0
Hungary	2.0	0.96
Rest of world	0.9	0.43

United Nations International Narcotics Control Board 2016 report: Narcotic Drugs
The four countries above comprise 96% of the 2016 estimated world requirements

Why did the FDA approve reformulated Opana ER in 2011 since it later concluded that the older version was not removed for safety reasons?

In order to suppress FDA approval of generic oxymorphone, Endo had petitioned the FDA in 2012 to conclude that the original Opana ER was removed for safety reasons. The FDA rejected this petition in May, 2013 concluding that "The available data do not support Endo's conclusion regarding purported safety advantages of OPR relative to OP."

The next slide shows FDA's evidence for this decision.

Early 2011 FDA evidence of increased OPR injection abuse potential

We disagree with Endo's conclusions about OPR's alleged safety advantages. While there is an increased ability of OPR to resist crushing relative to OP, data from in vitro and pharmacokinetic studies show that OPR's extended-release features can be compromised, causing the product to "dose dump," when subjected to other forms of manipulation such as cutting, grinding, or chewing, followed by swallowing.[14,15] It also

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appears that OPR can be prepared for insufflation (snorting) using commonly available tools and methods.[16] OPR can be readily prepared for injection, despite Endo's claim that OPR tablets have "resistance to aqueous extraction (i.e., poor syringeability)" (Petition at 4).[17] In addition, certain data suggest that OPR can more easily be prepared for injection than OP.[18]

May 2013 FDA memo, based on data available in 2011 before FDA approval of new version of Opana ER: FDA briefing package, pdf page 73-74

Findings from newer human abuse potential studies

“In the pivotal intranasal study EN3288-114, OPANA ER demonstrated an abuse-deterrent effect for the intranasal route of administration. This deterrent effect may help explain the lower frequency of abuse of reformulated OPANA ER via insufflation observed in the epidemiological data. An additional factor contributing to the intravenous abuse of reformulated OPANA ER tablets upon manipulation is the feasibility of obtaining suitable solutions for injection upon manipulation of the reformulated OPANA ER tablets.”

FDA Briefing package pdf pages 96-97

Findings from the post-marketing epi studies

"…the totality of the evidence is compelling that, among those abusing Opana ER, the reformulation caused a shift in non-oral routes from predominantly nasal to predominantly injection. The NAVIPPRO® study data provide evidence that such a shift occurred among Opana ER abusers being assessed for substance abuse treatment. Although a modest shift toward injection was seen among abusers of several comparator opioids across time periods, *a shift of this large magnitude was unique to Opana ER. (italics added)…* The RADARS® PC data also suggest a shift from the inhalation to injection route among Opana ER abuse cases identified through poison center calls."

FDA Briefing document, pdf page 177

Reasons why oral oxymorphone is not as preferable as by injection or as oral oxycodone and why injection oxymorphone may be more preferable

“The oral bioavailability of oxymorphone in humans is only approximately 10% (Endo 2011) compared to an intravenous dose of the same amount. In contrast, the oral bioavailability of oxycodone is 60% to 87% (Purdue 2016). As a result, oral administration of oxymorphone will result in lower plasma drug levels than oral administration of an equivalent amount of oxycodone and could contribute to the oral route being less preferred by individuals who abuse oxymorphone.”

FDA Briefing document, pdf page 96

1. **DISCUSSION:** Please discuss the strengths and limitations of the experimental and epidemiologic data regarding the safety concerns with reformulated Opana ER, including:

a. The observed shift in abuse patterns from the nasal to injection route of abuse, and
b. Reports of a TTP-like illness and HIV transmission associated with intravenous abuse of this drug

How do the data inform our understanding of the risk/benefit balance for Opana ER, relative to other oxymorphone products?

2. **DISCUSSION:** Please discuss any potential consequences of taking regulatory action(s) relating to reformulated Opana ER, such as effects on prescribing or abuse patterns for other products, including other oxymorphone products.

3. **VOTE**: Do the benefits of reformulated Opana ER continue to outweigh its risks? **NO**