Testimony of Sidney Wolfe, M.D.
Health Research Group of Public Citizen

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

ALO-O2: oxycodone/naltrexone

June 8, 2016

(I have no financial conflict of interest)

Embeda & ALO-02 Chronology

- Nov 2008 FDA pre approval Embeda AC meeting
- Aug 13 2009: Approved; no abuse deterrence stated in label
- Oct 8 2009 FDA warning letter about Embeda ad campaign: minimizing risk/making misleading abuse reduction claims
- Oct 21 2010 AC meeting on possible abuse reduction claim.
- March 1, 2011 Pfizer buys King
- March 11, 2011 Embeda recall due to naltrexone disint'grn
- Oct 2014 abuse reduction now in label
- 2019 completion dates for abuse reduction Embeda epi studies
- ALO-02 Wall Street "promise" and data from this meeting

Embeda & ALO-02 Chronology

- Nov 2008 FDA pre approval Embeda AC meeting
- Aug 13 2009: Approved; no abuse deterrence stated in label
- Oct 8 2009 FDA warning letter about Embeda ad campaign: minimizing risk/making misleading abuse reduction claims
- Oct 21 2010 AC meeting on possible abuse reduction claim.
- March 1, 2011 Pfizer buys King; " " from purchase, ??etc
- March 11, 2011 Embeda recall due to naltrexone disint'grn
- Oct 2014 abuse reduction now in label
- 2019 completion dates for abuse reduction Embeda epi studies
- ALO-02 Wall Street "promise" and data from this meeting

FDA vs Company Assessment of Abuse Potential for Embeda (11/14/08 AC briefing)

- **Alpharma: "The (IV) study suggests that the selected naltrexone to morphine ratio (1:25) provides an adequate reduction of abuse potential."**
- **"…no significant differences between ALO-01 whole and crushed on any subjective measure, suggesting a similar abuse potential whether ALO-01 is taken as directed (whole) or after tampering (crushed)."**
- **FDA: "Studies by the Sponsor demonstrate that under selected conditions, morphine can be efficiently extracted in isolation from naltrexone from EMBEDA™ capsules. Once extracted, the morphine could be subject to abuse by various routes of administration."**

Embeda & ALO-02 Chronology

- Nov 2008 FDA pre approval Embeda AC meeting
- Aug 13 2009: Approved; no abuse deterrence stated in label
- Oct 8 2009 FDA warning letter about Embeda ad campaign: minimizing risk/making misleading abuse reduction claims
- Oct 21 2010 AC meeting on possible abuse reduction claim.
- March 1, 2011 Pfizer buys King; " " from purchase, ??etc
- March 11, 2011 Embeda recall due to naltrexone disint'grn
- Oct 2014 abuse reduction now in label
- 2019 completion dates for abuse reduction Embeda epi studies
- ALO-02 Wall Street "promise" and data from this meeting

Violations stated in October 8, 2009 FDA Embeda Promotion Warning Letter

- "omits the information that "crushing, chewing, or dissolving the capsules results in a rapid release and absorption of a potentially **fatal** dose of morphine."

- " fail to reveal that co-ingestion of alcohol with EMBEDA may result in a potentially fatal overdose of morphine.

- "entirely fail to disclose the fact that the use of EMBEDA by opioid-naïve patients can cause **fatal** respiratory depression."

- "indicate that the EMBEDA capsules should not be crushed, chewed or dissolved, and go on to indicate that such tampering will result in the release of naltrexone, they fail to reveal the risk of precipitation of withdrawal in opioid-tolerant individuals associated with this naltrexone release."

Violations stated in October 8, 2009 FDA Embeda Promotion Warning Letter (cont'd)

"other serious adverse reactions associated with EMBEDA have been omitted from the promotional materials such as **respiratory arrest, apnea, circulatory depression, cardiac arrest, hypotension, and/or shock."**

- "The overall presentation of risk information….**grossly** minimizes the serious potential risks associated with EMBEDA."
- "unsubstantiated claims regarding the reduction in abuse liability with EMBEDA…misleading implication created by these presentations in the pieces that EMBEDA's properties result in abuse resistance and decreased abuse liability."

Embeda & ALO-02 Chronology

- Nov 2008 FDA pre approval Embeda AC meeting
- Aug 13 2009: Approved; no abuse deterrence stated in label
- Oct 8 2009 FDA warning letter about Embeda ad campaign: minimizing risk/making misleading abuse reduction claims
- Oct 21 2010 AC meeting on possible abuse reduction claim.
- March 1, 2011 Pfizer buys King; " " from purchase, ??etc
- March 11, 2011 Embeda recall due to naltrexone disint'grn
- Oct 2014 abuse reduction now in label
- 2019 completion dates for abuse reduction Embeda epi studies
- ALO-02 Wall Street "promise" and data from this meeting

FDA Presentation at 10/21/10 Embeda AC meeting

Formulation similar to Kadian (extended release morphine sulfate) approved in 1996

March 2005: Pre-IND meeting

Post marketing epidemiological studies

February 2008: original NDA for Embeda submitted

August 2009: Embeda was approved with REMS requirement

Discussions about the epidemiological program continued in post marketing

Pfizer's Proposed Schedule for Embeda Epi studies: Accepted by FDA in 2014

"The timetable you submitted on October 10, 2014, states that you will conduct this study according to the following schedule:

- Final Protocol Submission: 10/2015
-
- **Study Completion: 10/2019**

- Final Report Submission: 04/2020"

October 21 2010 FDA AC meeting

FDA presentation: Labeling Claims for an Abuse-Deterrent Product

"Would require demonstration that a product's abuse-deterrent properties studied in the pre-marketing program actually resulted in a reduction in abuse and its outcomes (death, overdose, and addiction), *as confirmed in post- marketing epidemiological studies*."

FDA Summary at 10/21/10 AC Meeting Discussing Embeda Abuse Deterrent Labeling

- "premarketing assessment of abuse deterrent formulations [information from *in vitro* manipulation/extraction studies, pharmacokinetic studies/ human abuse liability studies, provide information suggests how and to what extent a product, purported to be abuse deterrent, may be manipulated and abused once the product is on the market."
- "Only post-marketing epidemiological studies will reveal the extent to which a product, purported to be abuse deterrent, will actually be manipulated and abused after the product has been on the market."

10/21/10 AC Response to FDA question on evidence required for abuse deterrent label

…which studies, or elements of those studies, would most likely provide consistency in measurement. This is essential in that, as a regulatory body, the **Agency must provide a clear and consistent goal for companies requesting a determination of whether or not their product produces a clinically relevant reduction in abuse in the community that would support the inclusion of a claim of abuse-deterrence in the product label.**

> ***The majority of the committee felt that they would like to see the agency require both sponsors to specify the exact form of abuse or misuse that their product was designed to deter and then demonstrate efficacy of their strategy in a human population.***

The committee members advocated that the companies design outcomes using existing databases of monitoring on an every 6 month basis, for minimum study period of three years using a comparison to other similar products that are on the market.

Embeda & ALO-02 Chronology

- Nov 2008 FDA pre approval Embeda AC meeting
- Aug 13 2009: Approved; no abuse deterrence stated in label
- Oct 8 2009 FDA warning letter about Embeda ad campaign: minimizing risk/making misleading abuse reduction claims
- Oct 21 2010 AC meeting on possible abuse reduction claim.
- March 1, 2011 Pfizer buys King
- March 11, 2011 Embeda recall due to naltrexone disint'grn
- Oct 2014 abuse reduction now in label
- 2019 completion dates for abuse reduction Embeda epi studies
- ALO-02 Wall Street "promise" and data from this meeting

Embeda & ALO-02 Chronology

- Nov 2008 FDA pre approval Embeda AC meeting
- Aug 13 2009: Approved; no abuse deterrence stated in label
- Oct 8 2009 FDA warning letter about Embeda ad campaign: minimizing risk/making misleading abuse reduction claims
- Oct 21 2010 AC meeting on possible abuse reduction claim.
- March 1, 2011 Pfizer buys King; " " from purchase, ??etc
- March 11, 2011 Embeda recall due to naltrexone disint'grn
- Oct 2014 abuse reduction now in label
- 2019 completion dates for abuse reduction Embeda epi studies
- ALO-02 Wall Street "promise" and data from this meeting

10/17/14 FDA Letter to Pfizer Accompanying Permission to add Abuse Reduction to label

- "Conduct epidemiologic investigations to address whether the properties intended to deter misuse and abuse of EMBEDA (morphine sulfate and naltrexone hydrochloride extended-release capsules) actually result in a significant and meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the community. **The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of EMBEDA**."

Label additions concerning “reduce abuse” (“revised April 2014”)

- “The in vitro and pharmacokinetic data demonstrate that crushing EMBEDA pellets results in the simultaneous release and rapid absorption of morphine sulfate and naltrexone hydrochloride. These data along with results from the oral and intranasal human abuse potential studies **indicate that EMBEDA has properties that are expected to reduce abuse via the oral and intranasal route.** However, abuse of EMBEDA by these routes is still possible.”
- “A human abuse potential study of intravenous morphine and naltrexone to simulate crushed EMBEDA demonstrated lower Drug Liking and Drug High compared with morphine alone. However, it is unknown whether these results with simulated crushed EMBEDA predict a reduction in abuse by the IV route until additional post marketing data are available.”

Pfizer Proposed Schedule for Embeda Epi studies: Accepted by FDA

"The timetable you submitted on October 10, 2014, states that you will conduct this study according to the following schedule:

- Final Protocol Submission: 10/2015
-
- Study Completion: 10/2019

- Final Report Submission: 04/2020"

Embeda & ALO-02 Chronology

- Nov 2008 FDA pre approval Embeda AC meeting
- Aug 13 2009: Approved; no abuse deterrence stated in label
- Oct 8 2009 FDA warning letter about Embeda ad campaign: minimizing risk/making misleading abuse reduction claims
- Oct 21 2010 AC meeting on possible abuse reduction claim.
- March 1, 2011 Pfizer buys King; " " from purchase, ??etc
- March 11, 2011 Embeda recall due to naltrexone disint'grn
- Oct 2014 abuse reduction now in label
- 2019 completion dates for abuse reduction Embeda epi studies
- ALO-02 Wall Street "promise" and data from this meeting

Pfizer Informs Wall Street about ALO-02

Company Press Release, February 13, 2015*

"Abuse deterrent opioid medications incorporate technology designed to make the product difficult to abuse, yet when used appropriately, provide patients with intended pain relief. Pfizer believes that abuse deterrent formulation opioids, including ALO-02, are an important step toward helping to address the growing public health issue of opioid abuse in the U.S."

*http://www.pfizer.com/news/press-release/press-release-detail/pfizer_announces_fda_acceptance_for_review_of_a_new_drug_application_for_alo_02_oxycodone_hydrochloride_and_naltrexone_hydrochloride

FDA analysis of elective oxycodone or naltrexone extraction data for ALO-02

- **“moderate levels of naltrexone could be extracted in low volumes of solvent A (~5-10 ml) in relatively short periods under stress conditions.**

- **In conclusion, oxycodone is selectively extracted from intact ALO-02 pellets by a number of straightforward techniques. Common Solvents B to E appear to be capable of removing naltrexone selectively from crushed ALO-02. “**

Pfizer Statements on ALO-02

(from briefing documents)

- At time point 1, there was similar and nearly complete
- release of oxycodone and naltrexone in 30 of 31 solvents studied. In one solvent (M27) there was somewhat selective extraction of oxycodone from crushed pellets.
- In summary, after most physical and chemical challenges of ALO-02, the **formulation retained its abuse-deterrent features.**
- if the product is manipulated (eg, by crushing), naltrexone is released and acts as a competitive opioid antagonist at the mu opioid receptor, ***resulting in reduced abuse potential***.

FDA: “Lower risk of abuse” vs “meaningful reductions in abuse”

- **“[that] a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means rather, that the *risk of abuse is lower* than it would be without such properties.”**

- **Sponsors with approved AD language in the label are required to conduct post marketing *epidemiologic studies to determine whether the properties of their products result in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting.***

FDA 6/8/16 Briefing documents: Page 9

Conclusions

- **The FDA industry Guidance on "Abuse-Deterrent Opioids —Evaluation and Labeling" should be withdrawn and replaced with a regulation more favorable to patients than to opioid makers.**
- **ALO-02 should not be approved because of serious concerns about increased risk and abuse, given its easy manipulability.**
- **Current labeling for opioids with potentially abuse deterrent features, as specified in the Guidance, is too lax, literally encouraging companies to put in language that can easily be turned into promotional material increasing, not decreasing, use and abuse.**