

**Testimony Before the FDA's Drug Safety and
Risk Management & Anesthetic and Analgesic
Drug Products Advisory Committees regarding**

Oxycodogol: NKTR-181

January 14, 2020

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I have no financial conflicts of interest.

First Discussion Question: Did Nektar enroll an appropriate population, given guidelines concerning chronic low back pain (CLBP) opioid use?

- Guideline evaluation: The two *strong* ACP recommendations do not include the use of opioids. The *weak* third recommendation discusses opioids as a last resort, only if “the potential benefits outweigh the risks for individual patients.” (FDA brief, pp 13-14)
- FDA meeting with Nektar, October, 2017: “The sponsor was advised that previous advisory committees have raised concerns regarding utilizing a patient population for which opioids are not currently recommended as a mainstay of treatment (i.e., CLBP) and recommended that the Sponsor thoroughly document that the patient population enrolled is appropriate for opioid therapy.” (FDA brief, p 15)
- October 2019 *UpToDate* entry: opioid studies “for chronic and subacute low back pain rarely quantify the risk of important harms, such as abuse or addiction and have typically excluded patients at higher risk for these types of adverse events.”

Second Discussion Question: Are the data from the one efficacy study substantial enough to support an indication in patients with chronic low back pain who have not responded adequately to non-opioid and non-pharmacologic therapies?

- The consistent less than one-point difference on the 10-point pain scale for oxycodone vs placebo, though statistically significant, is not clinically meaningful. Two published reviews of this scale have stated the difference should be at least two points to be clinically meaningful.
- The National Academies' 2017 opioid report to the FDA discusses the benefit of using a positive comparator in addition to placebo.
- In a meta-analysis of randomized studies using opioids to treat chronic low back pain, the 4 studies assessing the efficacy of opioids compared with placebo or a nonopioid control did not show reduced pain with opioids. ($P= 0.136$).*

*Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med.* 2007;146(2):116-27

Third discussion question: Discuss concerns you may have about the safety profile of oxycodone. Include the given that patients may use oxycodone at doses higher than those for which adequate safety data are available.

The FDA noted that “NKTR-181 base and phosphate salt are controlled in Schedule II of the [Controlled Substances Act] for being a derivative of oxycodone” and that Nektar wishfully requested “a Schedule IV designation for the drug substance NKTR-181, however, based upon examination of information provided under NDA 211802, it is advisable to keep NKTR- 181 in Schedule II.” (FDA brief, p 20) Schedule II means the FDA considers NKTR to have the same abuse potential as oxycodone.

The actual use of higher doses in patients was tested by the company in study 12-181-5. The FDA found that “NKTR-181 dose 1200 mg, but not 400 mg or 600 mg, produced subjective effects (Drug Liking, High, Take Drug Again and Overall Drug Liking) comparable to that of oral 40 mg oxycodone, while all three doses of NKTR-181 showed some abuse potential above that of placebo. (FDA brief, p 22)

Third discussion question (cont'd)

- “The results of human abuse potential (HAP) Study 15-181-15 and the occurrence of adverse events are indicative of abuse potential in the clinical development program. NKTR-181 demonstrates an oral abuse potential comparable to oxycodone following oral administration. Results from Study 15-181-15 indicate that oxycodone, as a metabolite of NKTR-181, contributes in part to the subjective effects seen following oral administration of NKTR-181.” (FDA brief, p 20)
- “Oral 1200 mg NKTR-181 resulted in a maximum plasma concentration (C_{max}) for oxycodone of 40.8 ng/mL at 2.69 hours compared to C_{max} values of 60.4 ng/mL and 89.1 ng/mL, at 1.94 hours and 1.70 hours, respectively for oxycodone HCl 40 mg and 60 mg doses.” (FDA brief, p 22)

Discussion question 4: Considering the data that address the abuse potential of oxycodone, please discuss any concerns you have with the evaluation of its relative abuse liability and the potential impact of the abuse liability of this product on public health.

- The FDA has stated that there is a lack of data to establish whether there is either intravenous or intranasal abuse potential for oxycodone. (FDA brief, p 21)
- A previous study discussed public health concerns about the high prevalence of opioid use among patients for treatment of chronic back pain and the high rate of substance abuse among such patients.*

*Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med.* 2007;146(2):116-27

VOTE: Do you recommend approval of oxycodone?

- Because oxycodone has already caused tens of thousands of deaths and non-fatal damage to much larger numbers of other patients, is there really any need for yet another version of oxycodone, an opioid with an estimated 3.7 million people misusing it in 2017 according to National Survey on Drug Use and Health data?
- If your advisory committees or the FDA recommend approval of this new oxycodone-based drug---one that fails to provide clinically meaningful pain relief for chronic low back pain but has evidence of an oral abuse potential comparable to oxycodone---it would be a blow to hundreds of thousands of U.S. families tragically affected by previous oxycodone damage and would exemplify that the FDA is part of the problem instead of part of the solution.
- **The answer to this voting question must be an emphatic NO**