



Physicians for Responsible Opioid Prescribing  
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Stephen M. Hahn, M.D.  
Commissioner of Food and Drugs  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Re: FDA-2019-N-5552-0001: NDA 211802, Oxycodol (NKTR-181)  
*Submitted Electronically*

Dear Commissioner Hahn,

Physicians for Responsible Opioid Prescribing (PROP) is strongly opposed to approval of NDA 211802, oxycodol. We have three serious concerns regarding approval of oxycodol based on efficacy, safety, and proposed indication.

Efficacy: Evidence of oxycodol efficacy for chronic pain is lacking

Our review of materials for the Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee on January 14, 2020 shows that FDA requested two adequate and well-controlled clinical trials in order to show evidence of efficacy for oxycodol. **One of these two trials failed to demonstrate efficacy.** The second was neither adequate nor well-controlled because it utilized an enriched enrollment randomized withdrawal (EERW) study design. EERW is not appropriate for testing opioid analgesics because, prior to randomization, all subjects are made physiologically dependent on opioids in an open-label phase. Subjects randomized to placebo will experience withdrawal symptoms, including pain hypersensitivity. Comparing responses in subjects who remain on an opioid to subjects experiencing opioid withdrawal **skews results in favor of the opioid.** (Of note, post-acute opioid withdrawal symptoms can last several months).

In addition, results from EERW opioid trials are not generalizable to clinical practice because only patients who tolerate the opioid and found it helpful are enrolled in the placebo-controlled phase. About half of the subjects who initiated use of oxycodol were removed or dropped out from the study before the double-blind treatment phase began. The fact that oxycodol was poorly tolerated by nearly of enrolled subjects should not be ignored.

Safety: Evidence suggests that oxycodol is unsafe

In addition to the many known and serious adverse effects of opioids, oxycodol appears to have unique hepatotoxic effects. Study investigators were cautioned against rapid dose increases because of concern about hepatotoxicity. Nevertheless, 17 of 1691 subjects (in the Phase 2 and 3 studies), developed markedly elevated liver function tests. Nektar Therapeutics' proposed package insert (PI) recommends dose increases no more frequently than every 4 days to minimize the risk of liver inflammation.

We are especially concerned about the risk of liver failure in patients who may misuse oxycodol. In the 2015 National Survey on Drug Use and Health, 11.5 million Americans are estimated to have misused prescription opioids.<sup>1</sup> The most common motivation for misuse (63%) was to relieve physical pain. Individuals who misuse opioids are unlikely to follow the PI's recommendation for slow titration to avoid liver inflammation. We are also concerned about the unknown risks of oxycodol when misused by intranasal and injection routes.

Evidence about risks associated with misuse of oxycodol were not included in the meeting materials. We are especially troubled by this omission in light of a recommendation from the National Academy of Sciences (and endorsed by FDA) for including evidence on misuse when considering the risk benefit profile for drug approval.<sup>2</sup>

The inclusion of oxycodol in the FDA's Opioid Risk Evaluation and Mitigation Strategy (REMS) will not ensure that oxycodol's benefits outweigh its risks, as the REMS program intends. Despite initiation of the opioid REMS more than five years ago, the FDA and opioid manufacturers have not been able to demonstrate effectiveness of the REMS program.<sup>3</sup> Furthermore, educational messages in the REMS blueprint explicitly contradict opioid prescribing guidance issued by CDC, AHRQ and other federal agencies.

### Proposed Indication

If NDA 211802 is approved, Nektar Therapeutics will be authorized by FDA to promote oxycodol as safe and effective for the management of chronic low back pain. This indication explicitly contradicts opioid prescribing guidance from multiple federal agencies and professional societies. State and federal agencies and public health groups are actively engaged in efforts to discourage initiation of long-term opioids for non-structural low back pain and other chronic pain conditions. For example, in a 2016 statement, the CDC declared: "The science of opioids for chronic pain is clear: for the vast majority of patients, the known, serious, and too-often-fatal risks far outweigh the unproven and transient benefits."<sup>4</sup> In 2017, the Department of Veterans Affairs and the Department of Defense issued a practice guideline with a "strong" recommendation "against initiation of long-term opioid therapy for chronic pain."<sup>5</sup> The American College of Physicians and the American Academy of Neurology have similarly cautioned clinicians to avoid using opioids for low back pain. Allowing Nektar to advertise and promote a new branded opioid for chronic low back pain will hinder efforts by state and federal agencies to reduce initiation of long-term opioids.

It is our hope that the Advisory Committees and the FDA will reject the Nektar's oxycodol NDA.

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<sup>1</sup> Han B, Compton WM, Blanco C, et al. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Ann Intern Med.* 2017;167(5).

<sup>2</sup> Gottlieb A, Woodcock J. Marshaling FDA Benefit-Risk Expertise to Address the Current Opioid Abuse Epidemic. *JAMA.* 2017;318(5):421-422.

<sup>3</sup> Heyward J, Olson L, Sharfstein JM, et al. Evaluation of the Extended-Release/Long-Acting Opioid Prescribing Risk Evaluation and Mitigation Strategy Program by the US Food and Drug Administration. *JAMA Internal Medicine.* 2019, December 30.

<sup>4</sup> Frieden TR, Houry D. Reducing the Risks of Relief—The CDC Opioid-Prescribing Guideline. *N Engl J Med.* Doi: 10.1056.

<sup>5</sup> U.S. Department of Veterans Affairs, U.S. Department of Defense. Management of Opioid Therapy (OT) for Chronic Pain (2017) - VA/DoD Clinical Practice Guidelines.; 2017.