Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee
January 14, 2020

Location: FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), 10903 New Hampshire Ave, Silver Spring, Maryland.

Topic: The committees discussed new drug application 211802 for oxycodegol, a new molecular entity full mu-opioid receptor agonist, submitted by Nektar Therapeutics, for the management of chronic low back pain in adult patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The committees were asked to discuss the safety and efficacy data as well as the overall risk-benefit profile of the product.

These summary minutes for the January 14, 2020 joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration were approved on February 14, 2020.

I certify that I attended the January 14, 2020 joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Kalyani Bhatt
Acting Designated Federal Officer
AADPAC

/s/
Ronald Litman, DO, ML
Chairperson, AADPAC

Summary Minutes of the Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee
January 14, 2020

The Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) of the Food and Drug Administration, Center for Drug Evaluation and Research met on January 14, 2020, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Nektar Therapeutics. The meeting was called to order by Ronald Litman, DO, ML (Chairperson). The conflict of interest statement was read into the record by Kalyani Bhatt (Acting Designated Federal Officer). There were approximately 190 people in attendance. There were twelve (12) Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committees discussed new drug application 211802 for oxycodegol, a new molecular entity full mu-opioid receptor agonist, submitted by Nektar Therapeutics, for the management of chronic low back pain in adult patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The committees were asked to discuss the safety and efficacy data as well as the overall risk-benefit profile of the product.

Attendance:
Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting): Basavana G. Goudra, MD, FRCA, FCARSCI; Jennifer Higgins, PhD (Consumer Representative); Ronald S. Litman, DO, ML (Chairperson); Maura S. McAuliffe, CRNA, MSN, MSNA, PhD, FAAN; Mary Ellen McCann, MD, MPH; Abigail B. Shoben, PhD; Richard D. Urman, MD, MBA; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP; Lonnie Zeltzer, MD

Anesthetic and Analgesic Drug Products Advisory Committee Member Present (Non-Voting): Jay Horrow, MD, MS, FACC (Industry Representative)

Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting): Maryam Jowza, MD; Michael Sprintz, DO, DFASAM

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Karim Anton Calis, PharmD, MPH, FASHP, FCCP; Sonia Hernandez-Diaz, MD, MPH, DrPH**;** Steven B. Meisel, PharmD, CPPS; Suzanne B. Robotti (Consumer Representative)

Drug Safety and Risk Management Advisory Committee Member Present (Non-Voting): Reema J. Mehta, PharmD, MPH (Industry Representative)

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Denise M. Boudreau, PhD, RPh**;** Marie R. Griffin, MD, MPH; Laurel A. Habel, MPH, PhD**;** Martin Kulldorff, PhD**;** Anne-Michelle Ruha, MD, FACMT; Soko Setoguchi, MD, DrPH**;** Terri L. Warholak, PhD, RPh, CPHQ, FAPhA

Temporary Members (Voting): Jane B. Acri, PhD; Laura C. Block, PharmD, EMT-B (Patient Representative); Martin Garcia-Bunuel, MD; Traci C. Green PhD, MSc; Lee D. Hoffer, PhD, MPE; Timothy S. Lesar, PharmD; Brandon D.L. Marshall, PhD; Mara McAdams DeMarco, PhD; Paul Pisarik, MD, MPH; Friedhelm Sandbrink, MD; Maria E. Suarez-Almazor, MD, PhD; Patrick Sullivan, DVM, PhD; Linda S. Tyler, PharmD; Sherif Zaafran, MD, FASA

FDA Participants (Non-Voting): Mary Thanh Hai, MD**;** Rigoberto A. Roca, MD; Dominic Chiapperino, PhD; Judy Staffa, PhD, RPh; Joshua Lloyd, MD; Jennifer Nadel, MD

Acting Designated Federal Officer (Non-Voting): Kalyani Bhatt

Open Public Hearing Speakers: Robert L. Balster, PhD (Virginia Commonwealth University); Derek Muse, MD; Kelly E. Dunn, PhD; (Johns Hopkins University School of Medicine); Richard L. Montgomery, MD; Scott Whitt; Dolores Swan; Eva Agaiby, PharmD; Raymond Tidman, MD; Sidney M. Wolfe, MD (Public Citizen's Health Research Group); Kate Olsen; Diana Zuckerman, PhD (National Center for Health Research); Adriane Fugh-Berman, MD (Physicians for Rational Opioid Prescribing and PharmedOut)

The agenda was as follows:

Call to Order and Introduction of Committee	**Ronald S. Litman, DO, ML** Chairperson, AADPAC
Conflict of Interest Statement	**Kalyani Bhatt, BS, MS** Acting Designated Federal Officer, AADPAC
FDA Introductory Remarks	**Rigoberto A. Roca, MD** Acting Director Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) Office of Neuroscience (ON) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Nektar Therapeutics**
Introduction	**Steve Doberstein, PhD** Chief Scientist Nektar Therapeutics

APPLICANT PRESENTATIONS (CONT.)

What We Know About the Use of Opioids in Chronic Pain	**Nathaniel Katz, MD, MS** Chief Science Officer, WCG—Analgesic Solutions Associate Adjunct Professor of Anesthesia Tufts University School of Medicine
NKTR-181 Chemistry and Clinical Pharmacology	**Jonathan Zalevsky, PhD** Chief Research and Development Officer Nektar Therapeutics
Efficacy and Safety	**Margit Tagliaferri, MD** Vice President, Clinical Development Nektar Therapeutics
Abuse Potential	**Jonathan Zalevsky, PhD**
Clinical Perspective	**Jeffrey Gudin, MD** Clinical Associate Professor Department of Anesthesiology and Perioperative Medicine Rutgers New Jersey Medical School
Conclusion	**Steve Doberstein, PhD**
Clarifying Questions	

BREAK

FDA PRESENTATIONS

Regulatory and Clinical Context for the Evaluation of Oxycodegol	**Joshua Lloyd, MD** Clinical Team Leader DAAP, ON, OND, CDER, FDA
Drug Use and Abuse of ER/LA Opioids	**Cynthia Kornegay, PhD** Senior Epidemiologist Prescription Drug Abuse Team Division of Epidemiology II (DEPI-II) Office of Pharmacovigilance and Epidemiology (OPE) Office of Surveillance and Epidemiology (OSE)
Abuse Potential of Oxycodegol	**James Tolliver, PhD** Pharmacologist Controlled Substance Staff (CSS) Office of the Center Director (OCD), CDER, FDA **Shalini Bansil, MD** Medical Officer CSS, OND, CDER, FDA

FDA PRESENTATIONS (CONT.)

Clinical Efficacy and Safety Data Supporting Oxycodegol and Benefit-Risk Evaluation	**Jennifer Nadel, MD** Medical Officer DAAP, ON, OND, CDER, FDA
Clarifying Questions	
LUNCH	
Open Public Hearing	
Charge to the Committee	**Rigoberto A. Roca, MD**
Questions to the Committee/Committee Discussion	
BREAK	
Questions to the Committee/Committee Discussion (cont.)	
ADJOURNMENT	

Questions to the Committees:

1. **DISCUSSION:** Clinical practice guidelines state that opioids should not be used as the initial therapy for patients with chronic low back pain and should only be used when patients have not responded adequately to non-opioid and non-pharmacologic therapies. Discuss whether the Applicant enrolled an appropriate patient population.

   Committee Discussion*: The committees overall expressed concern that the enrolled population was not appropriate for opioid therapy. Many committee members expressed concern that either the patient population enrolled was inappropriate or at least the documentation was inadequate to show appropriateness. There was some concern expressed that there were no studies performed with an active comparator. There were a couple of panel members who felt the enrolled population was appropriate, considering patients would undergo a multi-modal treatment approach in clinical practice tailored to the needs of each patient; and therefore, it would be difficult to establish a population across a clinical study that reflected this approach. Please refer to the transcript for details of the Committees' discussion.*

2. **DISCUSSION:** The Applicant conducted one pivotal efficacy study. Given that oxycodegol is a full mu-opioid receptor agonist, discuss if the data from the one efficacy study are 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**.**

Committee Discussion: *The committee members who commented on this question agreed that one efficacy study was insufficient for approval citing, among other reasons, a small effect size and concerns over study design. One member brought up that over half of the patients titrated to the maximum dose and that there is not a clear understanding of what the highest dose should be. The panel members further noted that a characterization of the safety profile of oxycodegol had not been fully addressed and that the one efficacy study was not convincing enough to stand on its own to satisfy the usual requirement of at least two studies. Another member brought up the fact that every clinical practice guideline recommends against the use of opioids and noted concern that this product would be marketed as "the safe opioid." There were additional concerns related to how the drug will be marketed and whether the proper placebo/control group was used given that opioids are usually used in the context of other therapies. Please refer to the transcript for details of the Committees' discussion.*

3. **DISCUSSION:** Based on the available safety data, discuss any concerns you may have about the safety profile of oxycodegol, including whether there is evidence for potential hepatic toxicity. Discuss any recommendations you have for patient management regarding the liver safety findings. Given that patients may use oxycodegol at doses higher than those for which adequate safety data are available, discuss whether any additional data are needed to further inform the safety profile of oxycodegol.

   Committee Discussion: *A majority of the committee members were concerned about safety and potential liver toxicity, particularly in light of not having sufficient long-term safety data. In addition, concerns regarding the small number of patients exposed, as well as lack of data on co-administration with alcohol and effects of oral abuse and intravenous abuse of oxycodegol were raised. Some members recommended collecting additional safety data to further evaluate if there is a signal for liver toxicity.*

   Some of the panel members agreed there were adequate data to consider the benefit-to-risk ratio as favorable. However, they noted concerns as to whether the potential for liver toxicity could be addressed through post-market monitoring. Please refer to the transcript for details of the Committees' discussion.

4. **DISCUSSION:** Considering the data that have been provided that address the abuse potential of oxycodegol, 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.

   Committee Discussion: *The majority of the panel members were concerned that there was not enough data on the public health and abuse potential via all known routes of abuse. Additional concerns were raised about polysubstance abuse and possible delayed uptake could potentially result in an increased risk of overdose. Panel members also raised the question of whether adding more opioids could cause more overall health/safety issues to the general population. One panel member noted that oxycodegol may be favorable due to the*

possibility for less abuse potential mechanistically than oxycodone. The panel members generally agreed that more data are needed, particularly with regard to metabolites, and recommended that efficacy data coupled with data on safety need to be considered in tandem. Overall, the committee felt that there was not enough data on the impact on public health and the abuse potential of this drug. Please refer to the transcript for details of the Committees' discussion.

5. **VOTE:** Do you recommend approval of oxycodegol?
   A. Yes, for the proposed indication of management of chronic low back pain in adult patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
   B. Yes, for a general extended-release/long-acting opioid analgesic chronic pain indication.
   C. No

   Please discuss the rationale of your vote. If you voted A or B, please specify whether any post-approval studies should be required. If you voted C, please discuss what additional data are needed.

   Vote Result: A: 0 B: 0 C: 27

   ***Committee Discussion**: The committee voted unanimously against (27 to 0) the approval of oxycodegol due to deficiencies in the presented data. Many members felt that the potential benefits of this product did not outweigh its risks. Many were also concerned that, if this drug was approved, it could set a precedent for approval on just one efficacy study. Committee members were also concerned about the drug being marketed for chronic low back pain. Multiple members had concerns regarding insufficient knowledge about abuse via the intranasal and intravenous routes. Several members felt this drug was potentially promising, but it would need more efficacy and safety information first.*

   The additional data recommended by the committee members included the following:
   - *Toxicity data (e.g., signal for liver toxicity)*
   - *Data on abuse potential*
   - *Pharmacokinetic data at different doses along with inhibitors and inducers*
   - *An additional efficacy trial*
   - *Ethnic inclusion*
   - *Data on alcohol use with oxycodegol*
   - *Information on active metabolites*

   Please refer to the transcript for details of the Committees' discussion.

The meeting was adjourned at approximately 4:30 p.m.