

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the
Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the
Drug Safety and Risk Management Advisory Committee
June 26, 2018**

Location: DoubleTree by Hilton Hotel Bethesda - Washington DC, Grand Ballroom, 8120 Wisconsin Avenue, Bethesda, Maryland

Topic: The committees discussed new drug application 022324, oxycodone extended-release capsules, submitted by Pain Therapeutics, with the proposed indication of the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The product is intended to have abuse-deterrent properties based on its physicochemical properties. The committees were asked to discuss whether the data submitted by the Applicant are sufficient to support labeling of the product with the properties expected to deter abuse.

These summary minutes for the June 26, 2018 joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee of the Food and Drug Administration were approved on August 30, 2018.

I certify that I attended the June 26, 2018 joint meeting of the AADPAC and DSaRM of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/

Yinghua S. Wang, PharmD, MPH
Acting Designated Federal Officer
AADPAC

/s/

Mary Ellen McCann, MD, MPH
Acting Chairperson
AADPAC

June 26, 2018

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Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee
(AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)
June 26, 2018**

The 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, Center for Drug Evaluation and Research, met on June 26, 2018, at the DoubleTree by Hilton Hotel Bethesda - Washington DC, Grand Ballroom, 8120 Wisconsin Avenue, Bethesda, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Pain Therapeutics, Inc. The meeting was called to order by Mary Ellen McCann, MD, MPH (Acting Chairperson). The conflict of interest statement was read into the record by Yinghua Wang, PharmD, MPH (Acting Designated Federal Officer). There were approximately 100 people in attendance. There were five Open Public Hearing (OPH) 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 022324, oxycodone extended-release capsules, submitted by Pain Therapeutics, with the proposed indication of the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The product is intended to have abuse-deterrent properties based on its physicochemical properties. The committees were asked to discuss whether the data submitted by the Applicant are sufficient to support labeling of the product with the properties expected to deter abuse.

Attendance:

Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting): Raeford E. Brown, Jr., MD, FAAP (via phone); Basavana G. Goudra, MD, FRCA, FCARSCI; Mary Ellen McCann, MD, MPH (Acting Chairperson); Abigail B. Shoben, PhD; Lonnie Zeltzer, MD

Anesthetic and Analgesic Drug Products Advisory Committee Member Present (Non-Voting): W. Joseph Herring, MD, PhD (Industry Representative)

Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting): Brian T. Bateman, MD, MSc; Ronald S. Litman, DO, ML; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Marie R. Griffin, MD, MPH; Steven B. Meisel, PharmD, CPPS; Suzanne B. Robotti (Consumer Representative)

June 26, 2018

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting):

Kelly Besco, PharmD, FISMP, CPPS; Denise M. Boudreau, PhD, RPh; Laurel A. Habel, MPH, PhD; Sonia Hernandez-Diaz, MD, MPH, DrPH (Chairperson); Martin Kulldorff, PhD; Anne-Michelle Ruha, MD, FACMT; Soko Setoguchi, MD, DrPh; Terri L. Warholak, PhD, RPh, CPHQ, FAPhA

Drug Safety and Risk Management Advisory Committee Member Not Present (Non-Voting): Linda Scarazzini, MD, RPh (Industry Representative)

Temporary Members (Voting): Cynthia L. Arfken, PhD; Jeffrey Brent, MD, PhD; Daniel Ciccarone, MD, MPH; John B. Hertig, PharmD, MS, CPPS; Lewis S. Nelson, MD; Thomas E. Prisinzano, PhD; Jennifer M. Spotila, JD (Patient Representative); Gregory Terman, MD, PhD; Jon E. Zibbell, PhD

FDA Participants (Non-Voting): Sharon Hertz, MD; Judy Staffa, PhD, RPh; Lisa Wiltrout, MD

Acting Designated Federal Officer (Non-Voting): Yinghua S. Wang, PharmD, MPH

Open Public Hearing Speakers: Megan Polanin, PhD (National Center for Health Research); Ed Thompson (Pharmaceutical Manufacturing Research Services); Andrew Kolodny, MD (Physicians for Responsible Opioid Prescribing); Michael Daub and Alexia Holtum (Steve Rummeler Hope Network); Sidney M. Wolfe MD (Health Research Group at Public Citizen)

The agenda was as follows:

Call to Order and Introduction of Committee

Mary Ellen McCann, MD, MPH
Acting Chairperson, AADPAC

Conflict of Interest Statement

Yinghua Wang, PharmD
Acting Designated Federal Officer, AADPAC

FDA Introductory Remarks

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Office of Drug Evaluation II (ODE-II)
Office of New Drugs (OND), CDER, FDA

APPLICANT PRESENTATIONS

Pain Therapeutics, Inc.

Introduction

Remi Barbier
Founder and CEO
Pain Therapeutics, Inc.

In Vitro Abuse Deterrence

Michael Crowley, PhD
Acting Vice President, Drug Delivery Technologies
Pain Therapeutics, Inc.

June 26, 2018

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)

In Vivo Abuse Deterrence

Lynn Webster, MD

Vice President of Scientific Affairs, Neurosciences
PRA Health Sciences

Clinical Development

Nadav Friedmann, PhD, MD

Chief Operating and Medical Officer
Pain Therapeutics, Inc.

Excipient Safety

Stephen Montgomery, PhD

Regulatory and Toxicology Consultants, LLC

Risk Mitigation and Conclusion

Michael Marsman, PharmD

Senior Vice President, Regulatory Affairs
Pain Therapeutics, Inc.

Clarifying Questions

BREAK

FDA PRESENTATIONS

Category 3 Oral Study and Category 1
Smoking Study

James Tolliver, PhD

Pharmacologist
Controlled Substance Staff (CSS), CDER, FDA

Review of Recent Epidemiologic Data on
Use, Misuse and Abuse of Oxycodone

Mallika Mundkur, MD, MPH

Medical Officer
Division of Pharmacovigilance II (DPV-II)
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)
CDER, FDA

Remoxy ER: Multidisciplinary Review

Lisa Wiltrout, MD

Medical Officer
DAAAP, ODE-II, CDER, FDA

Clarifying Questions

LUNCH

Open Public Hearing

Charge to the Committee

Sharon Hertz, MD

Questions to the Committee/Committee
Discussion

BREAK

June 26, 2018

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)

Questions to the Committee/Committee
Discussion (cont.)

ADJOURNMENT

Question to the Committee:

1. **DISCUSSION:** Please discuss whether the Applicant has demonstrated that Remoxy ER (oxycodone extended-release capsules) has properties that can be expected to deter abuse, commenting on each of the following routes of abuse:
 - a. Oral
 - b. Nasal
 - c. Intravenous

Committee Discussion: The committee members agreed that Remoxy ER was not abuse deterrent by the oral route because patients can chew the capsules to produce blood levels close to that of crushed IR oxycodone tablets. Most committee members agreed that the Applicant demonstrated that Remoxy ER has properties that deter abuse via the nasal route. However, some committee members noted that while administering Remoxy ER nasally delivers less drug than with chewing and swallowing, it does not deter abuse because patients can use multiple doses. For the intravenous (IV) route, committee members were divided with regard to whether the Applicant demonstrated that Remoxy ER had intravenous (IV) abuse deterrent properties. Some members felt that the formulation is abuse deterrent while others cited that the conflicting results from the Applicant's and FDA's presentation cast doubt whether the IV formulation was abuse deterrent. One committee member noted the ingenuity of drug abusers and speculated that the method of preparation for IV administration would likely be discovered. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Please discuss whether there are sufficient data to support inclusion of language regarding abuse-deterrent properties in the product label for Remoxy ER, commenting on support for abuse-deterrent effects for each of the following routes of abuse:
 - a. Oral
 - b. Nasal
 - c. Intravenous

Committee Discussion: The committee discussion was similar to that for Question 1. Remoxy ER has no substantive oral abuse deterrent properties. The majority of those who commented stated that Remoxy ER had nasal abuse deterrent properties. There was a mixed response on whether Remoxy ER had IV abuse deterrent properties. Some committee members expressed that there was either conflicting or insufficient data to support including

June 26, 2018

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)

language regarding IV abuse deterrent properties in the product label. Please see the transcript for details of the committee discussion.

- DISCUSSION:** The Applicant is requesting approval of Remoxy ER as an analgesic with properties expected to deter abuse by the intravenous, and intranasal routes. Discuss whether you have any concerns regarding the impact of Remoxy ER on public health. Take into consideration its potential effect on abuse of extended-release oxycodone as well as potential consequences of administration of this product by unintended routes.

***Committee Discussion:** Regarding the impact of Remoxy ER on public health, one committee member stated that Remoxy ER is not useful for primary prevention since the disruption of the ER drug delivery mechanism by chewing the intact pills can lead to dose dumping, euphoria effects. The same committee member further stated that in terms of secondary prevention, those who are physically dependent on opioids will go to any lengths to extract the drug for use. Another committee member commented that the words “abuse deterrent” could create a false sense of security. It was also commented that one of the public health impacts of approving Remoxy ER could be that this product gets prescribed more frequently because of its “abuse deterrent” label. There was also concern about possible similarities between Remoxy ER and Opana ER where abuse deterrence via the nasal route increased abuse via the IV route with both expected (blood borne diseases) and unanticipated (thrombotic microangiopathy consequences). Some committee members were also concerned about the unknown risk of the excipients present in Remoxy ER, particularly when manipulated. Please see the transcript for details of the committee discussion.*

- VOTE:** Based on the data presented and the discussions about the data, do the efficacy, safety and risk-benefit profile of Remoxy ER support the approval of this application?

Vote Result: Yes: 3 No: 14 Abstain: 0

***Committee Discussion:** The majority of the panel members voted “No”, that the efficacy, safety and risk-benefit profile of Remoxy ER do not support the approval of this application. The committee members largely agreed that the public health risks of approving this reformulation of oxycodone does not outweigh its benefits. Other comments included that approving Remoxy ER with an abuse deterrent label may create a false sense of safety for this formulation and that the benefits of its nasal deterrence properties are not enough to justify approval with abuse deterrent labeling. Panelists voting “No” largely agreed that Remoxy ER did not demonstrate enough abuse deterrent properties via the oral and IV routes of administration. Of the committee members who voted “Yes,” the key comments were that the Applicant had met the standard for safety and efficacy and also met the criteria for abuse deterrence via the nasal and IV routes. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:22 p.m.