

**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
May 22, 2018**

Location: College Park Marriott Hotel and Conference Center, General Vessey Ballroom, 3501 University Blvd., Hyattsville, Maryland.

Topic: The committees were asked to discuss new drug application (NDA) 209588, for buprenorphine sublingual spray, submitted by INSYS Development Company, Inc., for the treatment of moderate-to-severe acute pain where the use of an opioid analgesic is appropriate. The committees will also be asked to discuss whether this product should be approved.

These summary minutes for the May 22, 2018, 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 were approved on July 5, 2018.

I certify that I attended the May 22, 2018, 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 and that these minutes accurately reflect what transpired.

_____/s/_____
Moon Hee V. Choi, PharmD
Designated Federal Officer, AADPAC

_____/s/_____
Almut Winterstein, RPh, PhD, FISPE
Chairperson, DSaRM

May 22, 2018

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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
May 22, 2018

The Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on May 22, 2018, at the College Park Marriott Hotel and Conference Center, General Vessey Ballroom, 3501 University Blvd., Hyattsville, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and INSYS Development Company, Inc. The meeting was called to order by Almut Winterstein, RPh, PhD, FISPE (Chairperson). The conflict of interest statement was read into the record by Moon Hee Choi, PharmD (Designated Federal Officer). There were approximately 85 people in attendance. There were two 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 were asked to discuss new drug application (NDA) 209588, for buprenorphine sublingual spray, submitted by INSYS Development Company, Inc., for the treatment of moderate-to-severe acute pain where the use of an opioid analgesic is appropriate. The committees were also asked to discuss whether this product should be approved.

Attendance:

Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting): Basavana G. Goudra, MD, FRCA, FCARSCI; Ronald S. Litman, DO, ML; Mary Ellen McCann, MD, MPH; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP; 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; Raeford E. Brown, Jr., MD, FAAP (Chairperson); Abigail B. Shoben, PhD

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Denise M. Boudreau, PhD, RPh; Steven B. Meisel, PharmD, CPPS; Suzanne B. Robotti (Consumer Representative); Anne-Michelle Ruha, MD, FACMT; Terri L. Warholak, PhD, RPh, CPHQ, FAPhA; Almut Winterstein, RPh, PhD, FISPE (Chairperson)

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Kelly Besco, PharmD, FISMP, CPPS; Niteesh K. Choudhry, MD, PhD; Laurel A. Habel, MPH, PhD; Christopher H. Schmid, PhD; Soko Setoguchi, MD, DrPh

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

Temporary Members (Voting): Chris Beyrer, MD, MPH; Phillip O. Coffin, MD, MIA, FACP; Nabarun Dasgupta, MPH, PhD; Randall Flick, MD, MPH; Elizabeth Joniak-Grant, PhD (Patient Representative); Alan Kaye, MD, PhD; Josiah “Jody” Rich, MD, MPH; Eric J. Tchetgen, PhD

FDA Participants (Non-Voting): Sharon Hertz, MD; Ellen Fields, MD, MPH; Tamra Meyer, PhD, MPH

Designated Federal Officer (Non-Voting): Moon Hee V. Choi, PharmD

Open Public Hearing Speakers: Sidney M. Wolfe MD (Health Research Group at Public Citizen); Megan Polanin, PhD (National Center for Health Research)

The agenda was as follows:

Call to Order and Introduction of Committee	Almut Winterstein, RPh, PhD, FISPE Chairperson, DSaRM
Conflict of Interest Statement	Moon Hee V. Choi, PharmD Designated Federal Officer, AADPAC
FDA Opening 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	INSYS Development Company Inc.
Introduction	Stephen Sherman, JD, MBA Senior Vice President, Regulatory Affairs and Clinical Development, Insys Development Co.
Medical Landscape and Unmet Need	Joseph Pergolizzi, MD Senior Partner and Director of Research Naples Anesthesia and Pain Associates, Florida
Development Rationale, Pharmacokinetics, Efficacy, and Safety	Dean Mariano, DO Senior Director of Clinical Development and Medical Affairs, Insys Development Co.
Risk Management	Stephen Sherman, JD, MBA
Benefit/Risk Assessment	Joseph Pergolizzi, MD

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Clarifying Questions

BREAK

FDA PRESENTATIONS

Clinical Overview

Robert Levin, MD
Clinical Reviewer
DAAAP, ODE-II, OND, CDER, FDA

Drug Utilization Analysis and
Assessment of Postmarket Abuse-
Related Issues

Cynthia Kornegay, PhD
Epidemiologist
Prescription Drug Abuse Team
Division of Epidemiology II (DEPI-II)
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)
CDER, FDA

Clarifying Questions

LUNCH

OPEN PUBLIC HEARING

Charge to the Committee

Sharon Hertz, MD

Questions to the Committee/
Committee Discussion

BREAK

Questions to the Committee/
Committee Discussion

ADJOURNMENT

Questions to the Committee:

- 1. DISCUSSION:** Discuss whether based on the available data, the efficacy findings support the indication “management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.” In your discussion, include any concerns regarding the time to onset of analgesia for Buvaya in the context of an acute pain indication. Consider each dose of Buvaya in your discussion.

Committee Discussion: Overall, the committee agreed that the efficacy findings were not sufficient, because of the delayed time to onset of analgesia, to support the indication of “management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.” The committee generally agreed that even

though there is a tremendous public health need for other alternative medications for acute pain, with a delayed time to onset and weak efficacy, Buvaya did not show clinical efficacy as a schedule III controlled substance and was compared to having similar efficacy as nonsteroidal anti-inflammatory drugs. In terms of each dose of Buvaya, the committee agreed that the 0.5 mg dose was marginally efficacious and that the two lower doses (0.25 mg and 0.125 mg) were ineffective for acute pain. Some committee members stated that they were not concerned about the onset of analgesia for Buvaya while other committee members noted safety concerns with re-dosing by patients with acute pain due to the slow time to onset. Please see the transcript for details of the committee discussion.

- 2. DISCUSSION:** Based on the available safety data, discuss whether the safety profile of Buvaya is acceptable for the proposed indication. Consider each dose of Buvaya in your discussion.

***Committee Discussion:** Based on the available safety data, the committee agreed that the safety profile of Buvaya is not acceptable for the proposed indication. Some committee members expressed concerns with the delayed time of onset of Buvaya and the potential for patients to take extra doses, and the potential for developing hypoxia after the patient is discharged and is no longer being monitored by a healthcare professional. Some committee members also expressed concerns with patients potentially using Buvaya in combination with another opioid product(s) due to the delayed time of analgesia onset (and possibly causing a cumulative effect) and these data were not available. Additionally, some committee members added that prescribers might think Buvaya is a safer product than a schedule II controlled substance, but in actuality, it may be less safe because of the risk of hypoxia. One committee noted the overdose potential of buprenorphine with ondansetron and concerns of QT prolongation (Torsades). Committee members expressed concern regarding the practicality of the sponsor's proposal to observe patients for development of hypoxia for 12 hours after the first dose. Some committee members also noted concerns regarding the high rate of nausea and vomiting with the 0.5 mg dose. Please see the transcript for details of the committee discussion.*

- 3. DISCUSSION:** Discuss any concerns you may have regarding the abuse or misuse of Buvaya and whether, based on the available data, the benefits to patients are expected to outweigh public health risks related to abuse and misuse.

***Committee Discussion:** Several committee members agreed that buprenorphine, the active ingredient in Buvaya, was generally seen as the safer and less abused option when compared to Schedule II opioid pain medications. These committee members added that the poor tolerability noted in the studies, the relatively low dose of buprenorphine (as compared to products used in medication assisted treatment [MAT] of opioid use disorder), the likely limited use of this product, and the high costs of a newly approved product are contributing factors that would make Buvaya less abused than some other opioid analgesic options. Other committee members noted concerns about the possible ease of tampering with the spray to access the vial containing the active ingredient of*

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Buvaya for abuse via an unintended route of administration. However, the dose of buprenorphine in this product is low compared to doses used for MAT. In terms of the misuse of Buvaya, some committee members noted concerns of re-dosing (and the risks associated with hypoxia) associated with the delayed time of onset as patients may perceive that either the product was administered incorrectly or that the desired effect was not achieved. Please see the transcript for details of the committee discussion.

4. **VOTE:** Overall, do the benefits of Buvaya outweigh the risks for the indication, “the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate,” supporting approval of Buvaya?

Vote Result: Yes: 1 No: 18 Abstain: 0

***Committee Discussion:** The majority of the committee voted “No”, that the benefits of Buvaya do not outweigh the risks for the indication, “the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate,” supporting approval of Buvaya. These members also agreed that although a commendable effort was made by the applicant to introduce an innovative product that may be less likely to be abused than some schedule II opioid analgesics, the factors contributing to their vote were the late onset of analgesia, and high rate of adverse events (primarily hypoxia. The committee member who voted “Yes” explained that the low abuse potential and the lack of alternative treatments available in the market were factors considered in the vote. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 2:56 p.m.