

**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
October 5, 2016**

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

Topic: The committees were asked to discuss naloxone products intended for use in the community, specifically the most appropriate dose or doses of naloxone to reverse the effects of life-threatening opioid overdose in all ages, and the role of having multiple doses available in this setting. The committees were also asked to discuss the criteria prescribers will use to select the most appropriate dose in advance of an opioid overdose event and the labeling to inform this decision, if multiple doses are available..

These summary minutes for the October 5, 2016, 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 October 31, 2016.

I certify that I attended the October 5, 2016, 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/
Jennifer Shepherd, RPh
Acting Designated Federal Officer, AADPAC

_____/s/
Raeford Brown, MD
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
October 5, 2016**

The following is the final report of the joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on October 5, 2016. A verbatim transcript will be available in approximately six weeks, sent to the Division of Analgesia, Anesthesia and Addiction Products and the Office of Safety and Epidemiology and posted on the FDA website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm486848.htm> and,
<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm486856.htm>.

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

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 October 5, 2016, at the FDA White Oak Campus, 10903 New Hampshire Avenue, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA, Adapt Pharma Operations Limited, Amphastar Pharmaceuticals, Inc., Insys Development Company, Inc., and Kaleo, Inc. The meeting was called to order by Raeford E. Brown, Jr., MD, FAAP (Chairperson). The conflict of interest statement was read into the record by Jennifer Shepherd, RPh (Acting Designated Federal Officer). There were approximately 150 people in attendance each meeting day. There were 14 Open Public Hearing (OPH) speaker presentations.

Issue: The committees were asked to discuss naloxone products intended for use in the community, specifically the most appropriate dose or doses of naloxone to reverse the effects of life-threatening opioid overdose in all ages, and the role of having multiple doses available in this setting. The committees were also asked to discuss the criteria prescribers will use to select the most appropriate dose in advance of an opioid overdose event and the labeling to inform this decision, if multiple doses are available.

Attendance:

Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting):

Brian T. Bateman, MD, MSc; Raeford E. Brown, Jr., MD, FAAP (Chairperson); David S. Craig, PharmD; Charles W. Emala Sr., MS, MD; Jeffrey L. Galinkin, MD, FAAP; Anita Gupta, DO, PharmD; Jennifer G. Higgins, PhD (Consumer Representative); Mary Ellen McCann, MD, MPH; Abigail B. Shoben, PhD

Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting):

Alan D. Kaye, MD, PhD; Rafael V. Miguel, MD

October 5, 2016

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

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

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Til Sturmer, MD, MPH, PhD; Terri L. Warholak, PhD, RPh, FAPhA; Almut G. Winterstein, RPh, PhD, FISPE

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Kelly Besco, PharmD, FISMP, CPPS; Niteesh K. Choudhry, MD, PhD; Tobias Gerhard, PhD, RPh; Anne-Michelle Ruha, MD, FACMT; Christopher H. Schmid, PhD; Andy S. Stergachis, PhD, RPh; Linda Tyler, PharmD, FASHP

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

Temporary Members (Voting): Francesa L. Beaudoin, MD, MS; Barbara Berney (Patient Representative); Jeffrey Brent, MD, PhD; Jonathan Davis, MD; Susan Fuchs, MD; Arthur F. Harralson, PharmD, BCPS; Mark L. Hudak, MD; Jane C. Maxwell, PhD; William J. Meurer, MD, MS; Lewis S. Nelson, MD; Ruth M. Parker, MD; Alexander A. Vinks, PharmD, PhD, FCP; Gary A. Walco, PhD; T. Mark Woods, PharmD, FASHP, BCPS; Victor Wu, MD, MPH; Athena F. Zuppa, MD

FDA Participants (Non-Voting): Sharon Hertz, MD; Judy Staffa, PhD, RPh; Joshua Lloyd, MD; LCDR Grace Chai, PharmD

Designated Federal Officer (Non-Voting): Jennifer Shepherd, RPh

Open Public Hearing Speakers: Dan Bigg (Chicago Recovery Alliance); Maya Doe-Simkins (Prescribe to Prevent); Hyun Namkoong, MPH (North Carolina Harm Reduction Coalition); Erin Haas, MPH (Maryland Department of Health and Mental Hygiene); Pam Lynch; Shoshanna Scholar (LA Community Health Project); Allan Clear (New York State Department of Health, AIDS Institute); Sharon Stancliff, MD (Harm Reduction Coalition); Hillary Kunins, MD (New York Department of Health and Mental Hygiene/Bureau of Alcohol & Drug Use Prevention, Care and Treatment); Jennifer Plumb, MD, MPH (Utah Naloxone); Erin Winstanley, PhD; Mark Lawson, MD (Mundipharma Research Ltd.); Celine Laffont, PhD (Indivior, Inc.); Susan Awad (American Society of Addiction Medicine)

The agenda was as follows:

Call to Order and Introduction of Committee

Raeford E. Brown Jr., MD, FAAP
Chairperson, AADPAC

Conflict of Interest Statement

Jennifer Shepherd, RPh
Acting Designated Federal Officer, AADPAC

October 5, 2016

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

FDA Introductory Remarks

Joshua Lloyd, MD
Clinical Team Leader
Division of Anesthesia, Analgesia and Addiction
Products (DAAAP)
Office of Drug Evaluation II (ODE-II)
Office of New Drugs (OND), CDER, FDA

INDUSTRY PRESENTATIONS

Adapt Pharma Operations Limited

Community Use Naloxone Dose

Seamus Mulligan, MS, BS
Chief Executive Officer
Adapt Pharma Operations Limited

Amphastar Pharmaceuticals, Inc.

Introduction, Agenda & Presenters

Jason Shandell, JD, MBA, Esq
President
Amphastar Pharmaceuticals, Inc.

Intranasal Off-Label Use of
IMS Naloxone Injection (2mg/2mL)
in Overdose Prevention Programs

Tony Marrs, MPH
Vice President, Clinical Operations
Amphastar Pharmaceuticals, Inc.

Development of Intranasal Naloxone

Robert Cormack, PhD
Senior Director, Regulatory Affairs
Amphastar Pharmaceuticals, Inc.

Insys Therapeutics, Inc.

Innovative Delivery Systems for Naloxone

Steve Sherman
Senior Vice President, Regulatory Affairs
Insys Therapeutics, Inc.

INDUSTRY PRESENTATIONS (CONT.)

kaléo, Inc.

Naloxone HCl Products for Use in the
Community Setting

Eric S. Edwards, MD, PhD
Vice President and Co-Founder
kaléo, Inc.

Clarifying Questions

BREAK

FDA PRESENTATIONS

Clinical and Regulatory Perspectives on
Naloxone Products Intended for Use in the
Community

Jennifer Nadel, MD
Medical Officer
DAAAP, ODE-II, OND, CDER, FDA

October 5, 2016

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

The Current Approach to Relative Bioavailability Studies in Support of Approval of New Naloxone Products

Yun Xu, PhD, MS
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology 2
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS), CDER, FDA

Drug utilization of naloxone

Shekhar Mehta, PharmD, MS
Drug Use Analyst
Division of Epidemiology II (DEPI-II)
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology (OSE)
CDER, FDA

Clarifying Questions

**CENTERS FOR DISEASE CONTROL
AND PREVENTION (CDC)
PRESENTATION**

Trends in Multiple Naloxone Administrations among EMS Personnel

Mark Faul, PhD, MA
Senior Health Scientist
Division of Unintentional Injury Prevention
National Center for Injury Prevention and Control
Centers for Disease Control and Prevention

Clarifying Questions

**LUNCH
OPEN PUBLIC HEARING**

Charge to the Committee

Sharon Hertz, MD
Director
DAAAP, ODE-II, OND, CDER, FDA

Questions to the Committee/
Committee Discussion

BREAK

Questions to the Committee/
Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSS:** The current pharmacokinetic standard for approval of naloxone products for use in the community requires demonstration of naloxone levels comparable to or greater than the levels achieved with the approved starting dose of 0.4 mg of naloxone injection administered by one of the approved, labeled routes of administration in adults [intravenous (IV), intramuscular (IM), or subcutaneous injection (SQ)], with a minimum of two doses packaged together.
 - a. Discuss whether matching or exceeding the naloxone exposure from a 0.4 mg injection of naloxone represents a high enough naloxone exposure to remain the basis for approval of novel products. Please take into consideration the variety of opioids that may be involved in an overdose in the community including: prescribed opioids vs. illicit opioids (heroin, heroin laced with fentanyl or carfentanyl); partial agonists vs. full agonists.
 - b. If you think a higher minimum naloxone level is more appropriate as the basis for approval of new products intended for use in the community, describe the target naloxone level and the rationale for this approach.
 - c. In controlled settings with trained health care providers and adequate ventilatory support, naloxone can be titrated to reverse an opioid overdose and minimize the risk for precipitating an acute withdrawal syndrome in an opioid-tolerant individual. In the community, trained health care providers and adequate ventilatory support may not be available, and naloxone may be administered by a layperson relying solely on the instructions for use that accompanies the naloxone product. In this latter setting, there is a 5- to 10-minute window before hypoxic injury becomes irreversible. Discuss how to balance the need for rapid reversal of an opioid overdose with the risk for precipitating an acute opioid withdrawal syndrome when selecting the minimum naloxone exposure that forms the basis for approval of novel products.

Committee Discussion: *The committee members did not come to a consensus on the appropriateness of a higher starting dose of naloxone versus the current dose. The committee members discussed that it is unclear what should be the basis to choose an absolute correct dose; however, the committee noted that the risk of not having a high enough dose is much greater than not having enough. Some committee members stated that there is concern that lower doses of naloxone might require rescuers to titrate, taking time, and risking further hypoxic injury to the patient. Many committee members stated that the risk of acute withdrawal is acceptable for the benefit of saving a patient. Please see the transcript for details of the committee discussion.*

2. **DISCUSS:** The approved dosing for known or suspected opioid overdose in adults is as follows: An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone hydrochloride have been administered, the diagnosis of

opioid induced or partial opioid induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

The approved dosing for known or suspected overdose in the pediatric population is as follows: The usual initial dose in pediatric patients is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered.

The past AAP recommendations for naloxone dosing in infants and children are as follows: 0.1 mg/kg for infants and children from birth to 5 years of age or 20 kg of body weight. Children older than 5 years of age or weighing more than 20 kg may be given 2.0 mg. These doses may be repeated as needed to maintain opiate reversal.

- a. Discuss whether the minimum exposure criterion (naloxone levels comparable to or greater than the levels achieved with 0.4 mg of naloxone injection) is appropriate for managing opioid overdose in children. If you do not think the standard is appropriate for children, discuss the criteria that should be used for naloxone products intended for use in children. Discuss whether the recommended criteria are suitable for use in adults.
- b. If different standards and resultant naloxone products are recommended for adults and children, one concern is that the presence of more than one naloxone product in a home may result in confusion about which product to administer in an emergency setting. Discuss how the risk of medication errors can be reduced in this setting.
- c. Discuss the need (if any) for PK and safety information in pediatric patients, depending on the route of administration and inactive ingredients, and any recommendations for how these data can be obtained.

Committee Discussion: *There was much discussion amongst the committee members concerning the need for trials to determine PK and PD data in children. The committee members stated that single products and simpler administration is important as is dosing information that can be used by those at reduced cognitive levels. The committee members stated that different standards do not seem to be necessary based on the limited data presented, and that the safety profile of naloxone is excellent based on forty years of history of safe use in even the tiniest infants. Some committee members discussed that PK and safety information in pediatric patients is not necessarily needed at this time. The committee members stated that if studies were done, they would most likely need to be done on postoperative patients receiving intravenous opioids and naloxone on an inpatient basis. The committee members also discussed some models of waiver of consent that could be possible and that the emergency waiver of consent model may also represent a design possibility but almost all studies would be inpatient because of the ethical concerns of studying children in extremis. Please see the transcript for details of the committee discussion.*

3. **VOTE:** Is the pharmacokinetic standard based on 0.4 mg of naloxone given by an approved route (IV, IM, SQ) appropriate for approval of naloxone products for use in the community or are higher doses and/or exposures required?

- a. Continue with the current minimum standard of comparable or greater exposure compared to 0.4 mg of naloxone injection
- b. Increase the minimum acceptable naloxone exposure to that comparable to or greater than a higher dose of naloxone injection

Vote Result: A: 13 B: 15

Committee Discussion: *A slight majority of the committee voted for “B”, in favor of increasing the minimum acceptable naloxone exposure to that comparable to or greater than a higher dose of naloxone injection. The committee members who voted to continue with the current minimum standard dose of naloxone stated that, as previously discussed, there was no indication that the current standard was failing the Agency or industry. Those voting for an increase opined that the current standard was set in 1971 and reflected inpatient use rather than use in the community where time to resuscitate may be minimal. These committee members also stated that given the wide availability of potent opioids in the community requiring multiple doses of naloxone, an increase in the minimum standard dose of naloxone seemed appropriate. Please see the transcript for details of the committee discussion.*

4. **VOTE:** Should there be different minimum standards used to support the approval of products intended for use in adults and in children?

Vote Result: Yes: 7 No: 21 Abstain: 0

Committee Discussion: *The majority of the committee members voted “No”, indicating that there should not be different minimum standards used to support the approval of products intended for use in adults and in children. Please see the transcript for details of the committee discussion.*

5. **DISCUSS:** Some Sponsors have proposed marketing more than one dose strength for their naloxone products intended for use in the community. When these strengths all meet or exceed the minimum naloxone exposure level set forth by the Agency, it is unclear what factors to describe in labeling to assist health care providers in making a decision to prescribe one dose strength over another.

Discuss what, if any, data Sponsors should provide to support the approval of more than one dose strength for any one naloxone product, and that can provide guidance to assist clinicians in dose selection.

Committee Discussion: *There was limited discussion due to time constraints, but a few committee members stated that there did not seem to be any support to encourage multiple dosage forms. Simplicity was the major reason given. Please see the transcript for details of the committee discussion.*

October 5, 2016

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

6. **DISCUSS:** As part of the standard for approval, naloxone products intended for use in the community have Instructions for Use (IFU) suitable for use by laypersons as supported by human factors studies and additional training is not required.
 - a. Discuss whether there is a role for new naloxone products intended for use in the community that requires training beyond the IFU.
 - b. Discuss the characteristics that should be considered for the study population enrolled in human factor studies of novel naloxone products. In particular, discuss the appropriate age range of study participants and whether the studies should specifically enroll adolescents, and if so, down to what minimum age. Also discuss whether these studies should specifically enroll caregivers of infants and children.

Committee Discussion: Question 6 was not discussed due to time constraints.

The meeting was adjourned at approximately 5:06 p.m.