

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

**Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee  
and the Drug Safety and Risk Management Advisory Committee Joint Meeting  
August 4, 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 discussed new drug application (NDA) 208603, morphine sulfate extended-release tablets, submitted by Egalet US Inc., 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. It has been formulated with the intent to provide abuse-deterrent properties. The committees also discussed 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 August 4, 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 11, 2016.

I certify that I attended the August 4, 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/  
Stephanie L. Begansky, PharmD  
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  
August 4, 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 August 4, 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.

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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 jointly on August 4, 2016, 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 Egalet, U.S., Inc. The meeting was called to order by Raeford Brown, MD, FAAP (Chairperson). The conflict of interest statement was read into the record by Stephanie Begansky, PharmD (Designated Federal Officer). There were approximately 100 people in attendance. There were 9 Open Public Hearing (OPH) speaker presentations.

**Issue:** The committees discussed new drug application (NDA) 208603, morphine sulfate extended-release tablets, submitted by Egalet US Inc., 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. It has been formulated with the intent to provide abuse-deterrent properties. The committees also discussed 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):** 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)

**Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting):** Rafael V. Miguel, MD; Abigail B. Shoben, PhD

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**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):**  
Tobias Gerhard, PhD, RPh

**Drug Safety and Risk Management Advisory Committee Members Not Present (Voting):**  
Kelly Besco, PharmD, FISMP, CPPS; Niteesh K. Choudhry, MD, PhD; Christopher H. Schmid, PhD; Andy S. Stergachis, PhD, RPh; Til Sturmer, MD, MPH, PhD; Linda Tyler, PharmD, FASHP; Almut G. Winterstein, RPh, PhD, FISPE

**Drug Safety and Risk Management Advisory Committee Member Present (Non-Voting):**  
Linda Scarazzini, MD, RPh (Industry Representative)

**Temporary Members (Voting):** Cynthia Arfken, PhD; Patrick Beardsley, PhD; Warren Bilker, PhD; Harriet de Wit, PhD; John Farrar, MD, MSCE, PhD; Randall Flick, MD, MPH; James Floyd, MD, MS; Scott Novak, PhD; Joseph O'Brien, MBA (Patient Representative); Sharon Walsh, PhD; Ursula Wesselmann, MD, PhD

**FDA Participants (Non-Voting):** Sharon Hertz, MD; Ellen Fields, MD, MPH; Judy Staffa, PhD, RPh

**Designated Federal Officer (Non-Voting):** Stephanie Begansky, PharmD

**Open Public Hearing Speakers:** Shruti Kulkarni (Center for Lawful Access and Abuse Deterrence); Dan Cohen (Abuse Deterrent Coalition); Sidney M. Wolfe, MD (Health Research Group at Public Citizen); Charlie Cichon (National Association of Drug Diversion Investigators); Edwin R. Thompson (Pharmaceutical Manufacturing Research Services, Inc.); Katie Duensing, JD (State Pain Policy Advocacy Network, Academy of Integrative Pain Management); Fred Brason II (Project Lazarus); Patricia Stouch; Adam Petersen

*The agenda was as follows:*

Call to Order and Introduction of Committee	<b>Raeford E. Brown, Jr., MD, FAAP</b> Chairperson, AADPAC
Conflict of Interest Statement	<b>Stephanie L. Begansky, PharmD</b> Designated Federal Officer, AADPAC
FDA Introductory Remarks	<b>Ellen Fields, MD, MPH</b> Deputy Director Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA

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**APPLICANT PRESENTATIONS**

**Egalet U.S., Inc.**

Introduction

**Robert Radie**

President and Chief Executive Officer  
Egalet Corporation

Public Health Need

**Richard C. Dart, MD, PhD**

Director  
Denver Health & Hospital Authority

Abuse-Deterrent Studies

**Jeffrey M. Dayno, MD**

Chief Medical Officer  
Egalet Corporation

Clinical Relevance

**Nathaniel Katz, MD, MS**

President, Analgesic Solutions  
Adjunct Assistant Professor of Anesthesia  
Tufts University School of Medicine

Clarifying Questions

**BREAK**

**FDA PRESENTATIONS**

Results of Oral Human Abuse  
Potential Study

**James M. Tolliver, PhD**

Pharmacologist  
Controlled Substance Staff  
Officer of Center Director  
CDER, FDA

Drug Utilization Patterns  
for Morphine Sulfate Extended-  
Release and Other ER/LA  
Opioid Analgesics 2011-2015

**Joann H. Lee, PharmD**

Drug Utilization Data Analyst  
Division of Epidemiology II  
Office of Pharmacovigilance and Epidemiology  
Office of Surveillance and Epidemiology  
CDER, FDA

Clarifying Questions

**LUNCH**

Open Public Hearing

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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. **DISCUSSION:** Please discuss whether there are sufficient data to support a finding that Arymo ER (morphine sulfate extended-release tablets) has properties that can be expected to deter abuse, commenting on support for abuse-deterrent effects for each of the three possible routes of abuse:
  - a. Oral
  - b. Nasal
  - c. Intravenous

*Committee Discussion:* It was the general consensus of the committee that there are sufficient data to support a finding of abuse-deterrent characteristics for the oral, nasal and intravenous routes of administration of Arymo ER. The committee stated that the phase one studies indicate extreme difficulty in reducing particle size and that Arymo ER could not easily be reduced to a size small enough for inhalation or snorting because of the hardness created through the manufacturing process. The committee also agreed that the small volume extraction showed limited removal of morphine for injection but large volume extraction studies did reveal the possibility of removal of relatively large amounts of morphine from the manufactured entity with some combinations of agents and conditions. Overall the committee stated that it appears that the nasal and intravenous abuse routes would be substantially reduced, along with the reduction in oral use by chewing. Please see the transcript for details of the committee discussion.

2. **VOTE:** If approved, should Arymo ER be labeled as an abuse-deterrent product by the oral route of abuse?

**Vote Result:**      Yes: 16              No: 3              Abstain: 0

*Committee Discussion:* The majority of the committee voted “Yes,” agreeing that Arymo ER should be labeled as an abuse-deterrent product by the oral route of abuse. Those who voted

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*“Yes” stated that there was sufficient evidence and clear data that chewing of the product is reduced by its abuse-deterrent properties. Those who voted “No” stated that the term “oral abuse-deterrent” was too broad for them to agree with and a narrower claim such as “not chewable” would be more acceptable. Please see the transcript for details of the committee discussion.*

3. **VOTE:** If approved, should Arymo ER be labeled as an abuse-deterrent product by the nasal route of abuse?

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

*Committee Discussion:* The majority of the committee voted “Yes,” stating that there was strong evidence that Arymo ER should be labeled as an abuse-deterrent product by the nasal route of abuse, and noted that this was supported through evidence of the challenges of physically manipulating the drug in addition to the human abuse potential studies. One committee member voted “No,” noting concerns about the large volume extraction possibility. Please see the transcript for details of the committee discussion.

4. **VOTE:** If approved, should Arymo ER be labeled as an abuse-deterrent product by the intravenous route of abuse?

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

*Committee Discussion:* The majority of the committee voted “Yes,” stating that Arymo ER should be labeled as an abuse-deterrent product by the intravenous route of abuse. One committee member voted “No,” noting concerns about the large volume extraction possibility. Please see the transcript for details of the committee discussion.

5. **VOTE:** Should Arymo ER be approved for the proposed indication, management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate?

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

*Committee Discussion:* The majority of the committee voted “Yes,” stating that Arymo ER should be approved for the proposed indication. One committee member added that there are populations, such as palliative care patients, that are in need of long-term opioid use and that it would be nice to have other options in the marketplace. The committee member who voted “No,” suggested that more information is needed on the solvents used to test this product and noted concerns for the potential of abuse of Arymo ER with some solvents. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 4:03 pm.