Location: Tommy Douglas Conference Center, 10000 New Hampshire Avenue, Silver Spring, Maryland.

Topic: On March 13 and 14, 2017, the committees discussed safety issues for new drug application (NDA) 201655, OPANA ER (oxymorphone hydrochloride) Extended-release Tablets, by Endo Pharmaceuticals Inc., with the indication of 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 an approved extended-release (ER) formulation intended to have abuse-deterrent properties based on its physicochemical properties, however, this information is not currently reflected in product labeling. The committees discussed pre- and post-marketing data about the abuse of OPANA ER, and the overall risk-benefit of this product. The committees also discussed abuse of generic oxymorphone ER and oxymorphone immediate-release (IR) products.

These summary minutes for the March 13-14, 2017, joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee of the Food and Drug Administration were approved on March 24, 2017.

I certify that I attended the March 13-14, 2017, joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products 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/
Almut Winterstein, PhD
Chairperson, DSaRM
The following is the final report of the joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee, held on March 13-14, 2017. A verbatim transcript will be available in approximately six weeks, sent to the Office of Safety and Epidemiology, the Division of Analgesia, Anesthesia and Addiction Products, and posted on the FDA website at:

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm486856.htm and

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm486848.htm.

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

The Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on March 13-14, 2017, at the Tommy Douglas Conference Center, 10000 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 Endo Pharmaceuticals Inc. The meeting was called to order by Almut G. Winterstein, RPh, PhD, FISPE (Chairperson). The conflict of interest statement was read into the record by Stephanie Begansky, PharmD (Designated Federal Officer). There were approximately 300 people in attendance on day 1 and approximately 150 people on day 2. There were 15 Open Public Hearing (OPH) speaker presentations.

**Issue:** The committees discussed safety issues for new drug application (NDA) 201655, OPANA ER (oxymorphone hydrochloride) Extended-release Tablets, by Endo Pharmaceuticals Inc., with the indication of 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 an approved extended-release (ER) formulation intended to have abuse-deterrent properties based on its physicochemical properties, however, this information is not currently reflected in product labeling. The committees discussed pre- and post-marketing data about the abuse of OPANA ER, and the overall risk-benefit of this product. The committees also discussed abuse of generic oxymorphone ER and oxymorphone immediate-release (IR) products.

**Attendance:**

**Drug Safety and Risk Management Advisory Committee Members Present (Voting):**
Tobias Gerhard, PhD, RPh; Suzanne B. Robotti (Consumer Representative); Anne-Michelle Ruha, MD, FACMT; Linda Tyler, PharmD, FASHP; Terri L. Warholak, PhD, RPh, 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; Christopher H. Schmid, PhD; Andy S. Stergachis, PhD, RPh; Til Sturmer, MD, MPH, PhD

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

Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting):
Brian T. Bateman, MD, MSc; Raeford E. Brown, Jr., MD, FAAP; David S. Craig, PharmD; Charles W. Emala Sr., MS, MD; 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): Jeffrey L. Galinkin, MD, FAAP; Alan D. Kaye, MD, PhD; Rafael V. Miguel, MD

Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Non-Voting): W. Joseph Herring, MD, PhD (Industry Representative) (via telephone on day 2)

Temporary Members (Voting): Jane B. Acri, PhD (via telephone on day 2); Warren B. Bilker, PhD; Daniel Ciccarone, MD, MPH; Marc G. Ghany, MD, MHSc; Ronald S. Litman, DO; Vincent Lo Re III, MD, MSCE; John Mendelson, MD; Laura D. Porter, MD (Patient Representative); Enrique F. Schisterman, PhD; Soko Setoguchi, MD, DrPH; James H. Woods, PhD; Eric D. Wish, PhD; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP

FDA Participants (Non-Voting): Sharon Hertz, MD; Ellen Fields, MD, MPH; Judy Staffa, PhD, RPh; Silvia N. Calderon, PhD; Jana McAninch, MD, MPH, MS

Open Public Hearing Speakers: Emily Walden; Shruti Kulkrani (Center for Lawful Access and Abuse Deterrence) – statement read by DFO; Bob Twillman, PhD (Academy of Integrative Pain Management); Wade Delk and Melanie Simpson (American Society for Pain Management Nursing); Edwin R. Thompson (Pharmaceutical Manufacturing Research Services, Inc.); Sid Wolfe (Public Citizen); Megan Polanain, PhD (National Center for Health Research Cancer Prevention and Treatment Fund); Dan Cohen (Abuse Deterrent Coalition); Brooks Bono – statement read by DFO; Orvalene Prewitt – statement read by DFO; Gail Cawkwell and Paul Coplan (Purdue Pharma); Andrew Kolodny (Physicians for Responsible Opioid Prescribing) – statement read by DFO; Joe Adams (National Physicians Alliance); Bob Twillman, PhD on behalf of Charles Argooff; Michael Lissner and Barbara Lissner – statement read by DFO

The agenda was as follows:

Day 1: Monday, March 13, 2017

Call to Order and Introduction of Committee
Almut Winterstein, RPh, PhD, FISPE
Chairperson, DSaRM

Conflict of Interest Statement
Stephanie L. Begansky, PharmD
Designated Federal Officer, AADPAC
FDA Introductory Remarks

Judy Staffa, PhD, RPh
Associate Director for Public Health Initiatives
Office of Surveillance and Epidemiology (OSE), CDER, FDA

INDUSTRY PRESENTATIONS

Endo Pharmaceuticals Inc.

Introduction

Harris Rotman, PhD
Vice President, US Regulatory Affairs
Endo Pharmaceuticals Inc.

Pain, Opioid Therapy, and Personalized Medicine

Perry G. Fine, MD
Professor of Anesthesiology
University of Utah

Decision-Making with Incomplete Observational Data

Alexander M. Walker, MD, DrPH
Principal
World Health Information Science Consultants

Post-Marketing Safety and Observational Data: Category 4 Abuse Epidemiology

Neil Shusterman, MD
Chief Medical Officer
Endo Pharmaceuticals Inc.

Epidemiology of Opana ER in Context

Richard C. Dart, MD, PhD
RADARS® System
Rocky Mountain Poison & Drug Center
Professor, University of Colorado

BREAK

Clarifying Questions

LUNCH

FDA PRESENTATIONS

Overview

Judy Staffa, PhD, RPh

Regulatory History of Opana ER

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

In Vitro Abuse Deterrent Studies of Opana ER

Erika E. Englund, PhD
CMC Reviewer
New Drugs Branch II (NDB-II)
Division of New Drug API (DNDAPI)
Office of New Drug Products (OND)
Office of Pharmaceutical Quality (OPQ), CDER, FDA

Intranasal Studies for Opana ER and Integration of In Vitro Findings

James M. Tolliver, PhD
Pharmacologist
Controlled Substance Staff (CSS), CDER, FDA
Drug Utilization Patterns for Oxymorphone ER and Selected Opioid Analgesics, 2009-2015

Corinne Woods, RPh, MPH
Drug Utilization Analyst
Division of Epidemiology II (DEPI-II)
Office of Pharmacovigilance and Epidemiology (OPE)
OSE, CDER, FDA

Clarifying Questions

GUEST SPEAKER PRESENTATION

The 2015 Indiana HIV Outbreak: Overview
Jerome Adams, MD, MPH
State Health Commissioner
Indiana State Department of Health

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC) PRESENTATION

CDC Outbreak Investigations Involving Opana ER
John T. Brooks, MD
Senior Medical Advisor
Division of HIV/AIDS Prevention
Centers for Disease Control and Prevention (CDC)

FDA PRESENTATIONS

Opana ER Adverse Event Reports: Non-Oral Abuse and Thrombotic Microangiopathy
Chaitali Patel, PharmD, BCPS
Safety Evaluator
Division of Pharmacovigilance II (DPV-II)
OPE, OSE, CDER, FDA

Mechanisms Underlying Thrombotic Microangiopathy Associated with Intravenous Opana ER Abuse
Ryan Hunt, MD
ORISE Fellow
Division of Plasma Protein Therapeutics (DPPT)
Office of Tissues and Advanced Therapies (OTAT)
Center for Biologics Evaluation and Research (CBER), FDA

Clarifying Questions

BREAK

FDA PRESENTATIONS

Statistical Considerations for Evaluating the Abuse-Related Outcomes of Reformulated Opana ER
Diqiong Xie, PhD
Mathematical Statistician
Division of Biometrics VII (DB-VII)
Office of Biostatistics (OB)
Office of Translational Sciences (OTS), CDER, FDA

Review of Postmarketing Epidemiologic Data on Opana ER and Selected Comparators
Jana McAninch, MD, MPH, MS
Medical Officer/Epidemiologist
DEPI-II, OPE, OSE, CDER, FDA

Clarifying Questions

ADJOURNMENT
**Day 2: Tuesday, March 14, 2017**

**Call to Order and Introduction of Committee**  
*Almut Winterstein, MD*  
Chairperson, DSaRM

**Conflict of Interest Statement**  
*Stephanie L. Begansky, PharmD*  
Designated Federal Officer, AADPAC

**FDA Introductory Remarks**  
*Judy Staffa, PhD, RPh*  
Associate Director for Public Health Initiatives  
Office of Surveillance and Epidemiology (OSE), CDER, FDA

**OPEN PUBLIC HEARING**

**LUNCH**

**Charge to the Committee**  
*Judy Staffa, PhD, RPh*

**Questions to the Committee/Committee Discussion**

**BREAK**

**Questions to the Committee/Committee Discussion (cont.)**

**ADJOURNMENT**

**Questions to the Committee:**

1. **DISCUSSION:** Please discuss the strengths and limitations of the experimental and epidemiologic data regarding the safety concerns with reformulated Opana ER, including:

   A. The observed shift in abuse patterns from the nasal to injection route of abuse, and

   B. Reports of a TTP-like illness and HIV transmission associated with intravenous abuse of this drug

   How do the data inform our understanding of the risk/benefit balance for Opana ER, relative to other oxymorphone products?

   **Committee Discussion:** The majority of the committee concurred that the totality of evidence shows that a shift in the abuse pattern of Opana ER from the nasal to injection route (IV) of abuse occurred following its reformulation. The committee agreed that the data demonstrate that reformulated Opana ER does not resist preparation for injection adequately, and represents a problem because of the apparent greater proportion of drug abuse by the injection route compared with other opioids. The committee also agreed that the high street cost of the product coupled with the method of preparation contributed to IV users sharing the drug solution and the equipment used to prepare and inject it, made worse by the large
number of injections per day. These factors likely contributed to the outbreak of HIV and 
HCV infections in Indiana. The committee agreed that cases of TTP-like illness in 
Tennessee were likely to have been specifically caused by intravenous exposure to the 
excipient, PEO. However, the committee stated the need for more and better epidemiological 
studies in the appropriate patient populations to quantify the risk of Opana ER. Regarding 
attributing the risks to reformulated Opana ER relative to other oxymorphone products, the 
committee stated that the current epidemiological data do implicate reformulated Opana ER, 
but emphasized that the studies suggest that oxymorphone ER generic products were also 
being abused at high rates by both the intranasal and IV routes. The committee suggested 
that cohort studies of users of Opana ER, and their response to the reformulation of the 
product, might have helped to make the data more compelling; however, the challenges of 
actually collecting such data were also noted. Please see the transcript for details of the 
committee discussion.

2. DISCUSSION: Please discuss any potential consequences of taking regulatory action(s) 
relating to reformulated Opana ER, such as effects on prescribing or abuse patterns for other 
products, including other oxymorphone products.

Committee Discussion: The committee concurred that patients abusing opioids will find 
something else to abuse if Opana ER is not available. They stated that the alternative might 
be safer than reformulated Opana ER in IV abusers, however, there was no way to predict 
the effects of regulatory actions. The committee agreed that generic oxymorphone ER 
products were also being abused by both the intranasal and IV routes. Several committee 
members questioned the role of Opana ER and oxymorphone in pain management, whilst 
several other committee members recommended that restrictions be placed on 
oxymorphone’s indication and prescribing, such as not to be prescribed as a first line 
therapy or that only certain physicians should be able to prescribe it to a defined subset of 
patients. Committee members suggested that restricting prescribing and patient access might 
in itself reduce street availability for abuse. Other committee members acknowledged that 
there are instances in pain management where use of oxymorphone is useful, such as patients 
with possible risks for pharmacokinetic drug-drug interactions. Several committee members 
noted that regulating the drug in terms of abuse potential versus the intended use of the 
product is difficult. Some committee members thought that a more specific risk evaluation 
and mitigation strategy (REMS) may decrease the risk of abuse and IV administration of this 
product, and oxymorphone products in general, whereas other committee members doubted 
the ability of either labeling or REMS to mitigate the risk of abuse and related adverse health 
effects. Please see the transcript for details of the committee discussion.

3. VOTE: Do the benefits of reformulated Opana ER continue to outweigh its risks?

Vote Result: Yes: 8  No: 18  Abstain: 1

Committee Discussion: The majority of the committee voted “No,” indicating their belief 
that the benefits of reformulated Opana ER do not continue to outweigh its risks. The 
committee members who voted “No” were split with regard to whether the unintended 
consequences associated with Opana ER were sufficient to warrant removal from the
Some members stated that, at the very least, a restrictive REMS should be put into place to limit prescribing. Those members who voted “Yes” acknowledged the risks with this formulation; however, also recognized that certain subpopulations of patients clearly benefit from this product being available on the market. The committee member who abstained stated that data were not provided to fairly evaluate the risk/benefit ratio of the product as most of the committee discussion surrounded only risk. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 5:10 p.m. on March 13, 2017 and 4:10 p.m. on March 14, 2017.