Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Joint
Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting
September 11, 2015

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

Topic: The committees discussed new drug application (NDA) 208090, oxycodone extended-release capsules for oral use, submitted by Collegium Pharmaceuticals, proposed for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative options are inadequate. This product has been formulated with the intent to provide abuse-deterrent properties. Pharmacokinetic data demonstrate that, in order to deliver the intended amount of oxycodone, the drug product must be taken with food. The committees also discussed the potential safety risks and the potential effects on efficacy associated with the extent of the food effect, and potential fluctuations in oxycodone levels that may occur if the product is not taken consistently with the same amount of food. In addition, the committees reviewed and discussed whether the data characterizing the abuse-deterrent properties support the likelihood that this drug product will have a meaningful effect on abuse and whether potential benefits to the public from abuse-deterrent properties outweigh potential risks to patients from the effect of food. The committees voted on whether this product should be approved for marketing in the United States.

These summary minutes for the September 11, 2015, 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 December 23, 2015.

I certify that I attended the September 11, 2015, 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/ ***/s/***

Stephanie L. Begansky, PharmD
Designated Federal Officer, AADPAC

Almut Winterstein, RPh, PhD, FISPE
Chairperson, DSaRM

Summary Minutes of the Joint
Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting
September 11, 2015

The following is a final report of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on September 11, 2015. 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/ucm433361.htm and http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm433818.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 September 11, 2015, 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. The meeting was called to order by Almut 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 150 people in attendance on September 11th. There were nine Open Public Hearing (OPH) speaker presentations.

Issue: The committees discussed new drug application (NDA) 208090, oxycodone extended-release capsules for oral use, submitted by Collegium Pharmaceuticals, proposed for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative options are inadequate. This product has been formulated with the intent to provide abuse-deterrent properties. Pharmacokinetic data demonstrate that, in order to deliver the intended amount of oxycodone, the drug product must be taken with food. The committees also discussed the potential safety risks and the potential effects on efficacy associated with the extent of the food effect, and potential fluctuations in oxycodone levels that may occur if the product is not taken consistently with the same amount of food. In addition, the committees reviewed and discussed whether the data characterizing the abuse-deterrent properties support the likelihood that this drug product will have a meaningful effect on abuse and whether potential benefits to the public from abuse-deterrent properties outweigh potential risks to patients from the effect of food. The committees voted on whether this product should be approved for marketing in the United States.

Attendance:

Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting): Brian T. Bateman, MD, MSc; Raeford E. Brown, Jr., MD, FAAP; Charles W. Emala Sr., MS, MD; Randall P. Flick, MD, MPH; Alan D. Kaye, MD, PhD; Rafael V. Miguel, MD; Abigail B. Shoben, PhD; Gary A. Walco, PhD

Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting): David S. Craig, PharmD; Jeffrey L. Galinkin, MD, FAAP; Jennifer G. Higgins, PhD

Anesthetic and Analgesic Drug Products Advisory Committee Member Present (Non-Voting): Richard L. Leff, MD (Industry Representative)

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Marjorie Shaw Phillips, MS, RPh, FASHP; Christopher H. Schmid, PhD; Linda Tyler, PharmD, FASHP; Almut G. Winterstein, RPh, PhD, FISPE (Chairperson)

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Niteesh K. Choudhry, MD, PhD; Jeanmarie Perrone, MD, FACMT; Tobias Gerhard, PhD, RPh; Karen M. Hopkins, MD; Andy S. Stergachis, PhD, RPh; Til Sturmer, MD, MPH, PhD

Drug Safety and Risk Management Advisory Committee Member Not Present (Non-Voting): Patrizia Cavazzoni, MD

Temporary Members (Voting): Nananda Col, MD, MPP, MPH; Anita Gupta, DO, PharmD; Arthur F. Harralson, PharmD, BCPS; Arthur H. Kibbe, RPh, PhD; James J. Kiefert, EdD (Patient Representative); Edward Michna, MD, JD, RPh; Elaine H. Morrato, DrPH, MPH, CPH; Steven D. Passik, PhD; Estela M. Pledge, MSEd, LCPC NCC, ACS, MAC (Acting Consumer Representative); Sharon L. Walsh, PhD; Michael S. Wolf, PhD, MPH

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

Open Public Hearing Speakers: Ellen Smith (US Pain Foundation); Dana Saffel, PharmD, CPh, CGP (PharmaCare Strategies, Inc.); Heather McLaughlin (National Association of Drug Diversion Investigators); Rob Goldsmith (Cancer Support Community); Bob Twillman, PhD (American Academy of Pain Management); Joan Baird, PharmD on behalf of Frank Grosso (American Society of Consultant Pharmacists); Janice Brewer; Marcus Garza on behalf of Michael Barens, Esq. (Center for Lawful Access and Abuse Deterrence); Stacey Worthy, Esq. (Alliance for Adoption of Innovations in Medicine)

The agenda was as follows:

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
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	**Collegium Pharmaceutical, Inc.**
Introduction	**Michael Heffernan, RPh** Founder and Chief Executive Officer Collegium Pharmaceutical, Inc.
Medical Need	**Bill McCarberg, MD** Elizabeth Hospice and Neighborhood Healthcare
Abuse-Deterrence Studies	**Alison Fleming, PhD** Vice President, Product Development Collegium Pharmaceutical, Inc.
Efficacy and Safety	**Ernest Kopecky, PhD, MBA** Vice President, Clinical Development Collegium Pharmaceutical, Inc.
Clinical Pharmacology and Food Effect	**Nicholas Fleischer, RPh, PhD** Vice President The Weinberg Group, Inc.
Risk Management	**Michael Heffernan, RPh**
Benefit-Risk Profile	**Nathaniel Katz, MD, MS** President Analgesics Solutions
Clarifying Questions	
BREAK	

FDA PRESENTATIONS

Food Effect with Xtampza ER	**Srikanth C. Nallani, PhD** Clinical Pharmacology Reviewer Division of Clinical Pharmacology II Office of Clinical Pharmacology Office of Translational Sciences, CDER, FDA
Results of the Oral Human Abuse Liability Study	**James M. Tolliver, PhD** Pharmacology Reviewer Controlled Substance Staff, CDER, FDA
Clinical Implications of Xtampza ER's Food Effect	**Ellen W. Fields, MD, MPH** Clinical Team Leader DAAAP, ODE II, OND, CDER, FDA

SPEAKER PRESENTATION

Patient-Centered Rx Communication: Strategies to Mitigate/Minimize Risk	**Michael S. Wolf, PhD, MPH** Professor, Medicine and Learning Sciences Associate Chair, Department of Medicine Associate Division Chief - Research General Internal Medicine & Geriatrics Feinberg School of Medicine Northwestern University Chicago, Illinois

Clarifying Questions

LUNCH

Open Public Hearing

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the pharmacokinetic data presented which describe the effect of food on the extent of absorption of oxycodone from XTAMPZA ER and discuss what, if any, clinical consequences for safety or efficacy may result from the food effect.

   Committee Discussion: *The committee recognized that the pharmacokinetic (PK) data analyzed the effect of food on a single dose of XTAMPZA ER, and noted that in real-world*

use, XTAMPZA ER would be dosed chronically at steady state which lessens the risk of the food effect. The committee discussed the possibility of a patient taking XTAMPZA ER on an empty stomach, which would result in lower overall exposure to oxycodone, which from a safety perspective is not as concerning as a food effect that increases drug concentrations. The committee stated that they were reassured with the 65,000 doses recorded in a phase III clinical trial that showed a lack of difference in efficacy across meal patterns based on the Sponsor's analyses, even though meal pattern categorization may not have been specific enough to pick up effects. Overall, the committee acknowledged the food effect but was not concerned with its clinical consequences for safety or efficacy. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Discuss whether labeling instructions to take XTAMPZA ER with food are sufficient to mitigate the risk of adverse clinical consequences, if any, identified in the prior discussion. In particular, given that in general, opioids are dosed without regard to food, discuss whether instructions in the package insert are sufficient to result in correct prescribing instructions and use of XTAMPZA ER.

   Committee Discussion: *The committee was split on whether instructions in the labeling are sufficient to mitigate the risk of adverse clinical consequences as a result of incorrect prescribing instructions and use of XTAMPZA ER. Some committee members noted that the labeling instructions were sufficient because chronic pain patients would be very likely to comply with instructions to take with food because it results in greater efficacy and because administration times can be planned. Other members of the committee stated that labeling recommendations could be more specific and more could be done with the packaging to signal to the patient or their caregiver that XTAMPZA ER is to be given with food. It was suggested by one committee member to provide language or visualization on blister packaging to indicate that it should be taken with food. The committee also discussed the benefits of being able to sprinkle the contents of the capsule on applesauce. The committee noted that the abuse-deterrent properties of this formulation prevent dose-dumping if the capsule is accidentally chewed or crushed. Overall, the committee agreed that the food effect should remain in the label. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Discuss whether the data show that XTAMPZA ER's abuse-deterrent properties can be expected to result in a meaningful reduction in abuse.

   Committee Discussion: *The committee was in agreement that XTAMPZA ER's abuse-deterrent properties exhibited advancement in abuse reduction, in comparison to currently available technology. The committee discussed the "drug-liking" scores and stated that they did not differ greatly beyond that of the comparator, but this product is a step forward due to the lack of dose dumping when chewed, which may deter oral abuse or misuse, and the intranasal and intravenous abuse-deterrent properties. The committee applauded the applicant for creating a medication with abuse- deterrent properties that also allowed it to be used in populations that have difficulty swallowing. Overall, the committee agreed that there is not likely to be a large impact on public health in terms of XTAMPZA's impact on opioid abuse and substance use disorders, but the abuse-deterrent properties of XTAMPZA ER may curb abuse and misuse at the individual level and improve safety, especially for*

patients with difficulty swallowing. Please see the transcript for details of the committee discussion.

4. **DISCUSSION:** Discuss whether the potential benefits from the abuse-deterrent properties of XTAMPZA ER outweigh the potential risk resulting from the effect of food on the absorption of oxycodone from XTAMPZA ER.

   Committee Discussion: *The committee agreed that the potential benefits from the abuse-deterrent properties of XTAMPZA ER outweigh the potential risk resulting from the effect of food on the absorption of oxycodone from XTAMPZA ER. The committee stated that the abuse-deterrent properties were well-thought out and could make the product safer on the individual level. Additionally, the committee was impressed with XTAMPZA ER's ability to safely be chewed or sprinkled on applesauce for patients with dysphagia. Please see the transcript for details of the committee discussion.*

5. **VOTE:** Should XTAMPZA ER be approved for marketing in the US?

   Vote: Yes = 23 No = 0 Abstain = 0

   Committee Discussion: *The committee unanimously agreed that XTAMPZA ER's abuse-deterrent properties exhibited an improvement over currently available technology. Additionally, the committee agreed that irrespective of the abuse-deterrent properties, XTAMPZA ER would be a great option for patients with dysphagia. It was unanimously agreed that XTAMPZA ER should be approved for marketing in the US. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:30 p.m. on September 11, 2015.