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 10, 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) 206830, oxycodone immediate-release tablets, submitted by Purdue Pharma, with the proposed indication of the management of moderate to severe pain where the use of an opioid analgesic is appropriate. It has been formulated with the intent to provide abuse-deterrent properties. The pharmacokinetic data demonstrate that there is a significant food effect resulting in a significant delay in absorption and peak plasma concentration of oxycodone when taken with food. The Applicant proposes to address this finding by labeling the product to be taken on an empty stomach, but patients may have difficulty complying with these instructions as the product is dosed every 4 to 6 hours as needed. The committees discussed the potential safety risks and the potential effects on efficacy associated with the delayed peak concentration when taken with food, and the feasibility of labeling to be taken an empty stomach as a means to mitigate the potential risks. The committees also considered whether the potential public health benefit of the product's abuse-deterrent properties are sufficient to outweigh the risk to patients who are prescribed the product for the management of pain.

These summary minutes for the September 10, 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 October 26, 2015.

I certify that I attended the September 10, 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	Almut Winterstein, RPh, PhD, FISPE
Designated Federal Officer, AADPAC	*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 10, 2015

The following is the final report of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on September 10, 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 10, 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 and Purdue Pharma. 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 100 people in attendance on September 10th. There were three Open Public Hearing (OPH) speaker presentations.

Issue: The committees discussed new drug application (NDA) 206830, oxycodone immediate-release tablets, submitted by Purdue Pharma, with the proposed indication of the management of moderate to severe pain where the use of an opioid analgesic is appropriate. It has been formulated with the intent to provide abuse-deterrent properties. The pharmacokinetic data demonstrate that there is a significant food effect resulting in a significant delay in absorption and peak plasma concentration of oxycodone when taken with food. The Applicant proposes to address this finding by labeling the product to be taken on an empty stomach, but patients may have difficulty complying with these instructions as the product is dosed every 4 to 6 hours as needed. The committees discussed the potential safety risks and the potential effects on efficacy associated with the delayed peak concentration when taken with food, and the feasibility of labeling to be taken an empty stomach as a means to mitigate the potential risks. The committees also considered whether the potential public health benefit of the product's abuse-deterrent properties are sufficient to outweigh the risk to patients who are prescribed the product for the management of pain.

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; 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): Randall P. Flick, MD, MPH ; 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): Niteesh K. Choudhry, MD, PhD; Jeanmarie Perrone, MD, FACMT; 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): 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); Elaine H. Morrato, DrPH, MPH, CPH; Ruth M. Parker, MD; 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: Steve Cline (Partnership for Drug-Free Kids); Michael Giuliani, MD (Mallinckrodt Pharmaceuticals); Marcus Garza on behalf of Michael Barens, Esq. (Center for Lawful Access and Abuse Deterrence)

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	**Purdue Pharma L.P.**
Introduction	**Richard Fanelli, PhD** Head of Regulatory Affairs Purdue Pharma L.P.
Need for an Abuse Deterrent Immediate-Release Oxycodone Formulation	**Laura Wallace, MPH** Director, Risk Management & Epidemiology Purdue Pharma L.P.
In Vitro Abuse Deterrence Assessment of Avridi Tablets	**Jennifer Giordano** Director, Analytical Sciences Purdue Pharma L.P.
Avridi Intranasal Abuse Potential and Avridi Bioequivalence Evaluation	**Alessandra Cipriano, MSHS** SR Clinical Research Scientist Clinical Pharmacology Purdue Pharma L.P.
Avridi Pharmacokinetic Modeling	**Stephen Harris, MD** Executive Medical Director Clinical Pharmacology Purdue Pharma L.P.
Risk Management and Summary	**Laura Wallace, MPH**
Clarifying Questions	
BREAK	
FDA PRESENTATIONS	
Food Effect	**Srikanth C. Nallani, PhD** Clinical Pharmacology Reviewer Division of Clinical Pharmacology II Office of Clinical Pharmacology Office of Translational Sciences, CDER, FDA

FDA PRESENTATIONS (CONT.)

Clinical Implications of Avridi's Food Effect	**Jacqueline Spaulding, MD, MPH** Medical Officer 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 absorption time for oxycodone from AVRIDI and discuss what, if any, clinical consequences for safety or efficacy may result from the food effect.

   Committee Discussion: *With respect to the pharmacokinetic (PK) data presented in relation to the effect of food on the delayed absorption time for oxycodone from AVRIDI, the committee had concerns regarding the potential lack of efficacy and the increased risk of oxycodone overdose. Many committee members stated that the potential for misuse by taking AVRIDI with food was a major concern because it would be difficult for patients to anticipate when pain relief was needed, and if taken regularly, to schedule food intake with a 4 to 6 hours dosing schedule. The committee agreed that patients expect an immediate release (IR) opioid product to give rapid pain relief and patients may take more than one dose if the first dose is not effective, which may result in higher than intended blood concentrations and side effects such as respiratory depression. Committee members also stated that the addition of other medications may result in a compounded safety concern due*

to the nature of the PK data. The committee expressed concern with the lack of PK data beyond 7 – 8 hours. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Discuss whether instructions to take AVRIDI every 4 to 6 hours on an empty stomach are feasible, and whether patients are likely to comply.

   Committee Discussion: *The committee agreed that the instructions to take AVRIDI every 4 to 6 hours on an empty stomach would be very difficult for patients to comply with. The definition of an empty stomach was discussed and panel members agreed that such a definition can vary widely and may lead to errors in medication administration, a lack of efficacy, and the potential for overdose. One panel member stated that with the frequent dosing of every 4 to 6 hours on an empty stomach, patients would have limited opportunities to eat. Another panel member stated that concomitant medications may increase the problem in scheduling administration of this medication since some medications must be taken with food and this one would be taken on an empty stomach. Overall, the committee agreed that it would be highly unlikely for patients to be able to follow the instructions completely and accurately. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Discuss whether labeling instructions to take AVRIDI on an empty stomach 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 AVRIDI.

   Committee Discussion: *The committee concluded that the proposed labeling instructions to take AVRIDI on an empty stomach are not sufficient to mitigate the risk of adverse clinical consequences due to incorrect prescribing instructions or improper medication use. Committee members discussed evidence showing that most package inserts are thrown away and auxiliary labels are often ignored. One committee member who works with chronic pain patients stated that these patients most likely will take this medication whenever they have breakthrough pain to get immediate relief and will not pay much attention to the warning of taking it on an empty stomach or the consequences of failing to do so. The committee agreed that, at minimum, an enhanced warning or labeling system should be put into place for effective risk communication. Please see the transcript for details of the committee discussion.*

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

   Committee Discussion: *The committee members agreed that AVRIDI's abuse-deterrent properties exhibited, at best, incremental improvement over currently marketed products. The committee acknowledged that there was significant evidence to deter intravenous (IV) and intranasal abuse on an individual basis. The committee members noted that AVRIDI can still be abused orally and that larger scale operations or those with advanced knowledge could easily extract oxycodone around the abuse-deterrent properties. The committee also agreed that the abuse-deterrent properties were unlikely to have a meaningful impact on*

overall public health because abusers would simply choose to avoid this product and use another oxycodone product. Please see the transcript for details of the committee discussion.

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

   Committee Discussion: *The committee acknowledged the evidence demonstrating the incremental improvement in preventing IV and intranasal abuse due to the abuse deterrent properties of AVRIDI. However, the committee stated that new abuse deterrent medications need to display equal efficacy and safety in comparison to currently marketed products with the added benefit of abuse deterrence. The committee noted that AVRIDI's food effect resulted in it being an inferior product from both an efficacy and safety standpoint. They were also concerned that there was a lack of clinical data describing how patients will use the drug and if they would be able to follow instructions to take on an empty stomach. Overall, the committee agreed that the large efficacy and safety concern of needing to take AVRIDI with food far outweighed the minimal potential benefit of its abuse deterrent properties. Please see the transcript for details of the committee discussion.*

6. **VOTE:** Should AVRIDI be approved for marketing in the US?

   Vote: Yes = 1 No = 23 Abstain = 0

   Committee Discussion: *The vast majority of the committee agreed that AVRIDI should not be marketed in the US. The members who voted "No" noted safety concerns if it is not taken on an empty stomach and that the data indicated that there would be a great potential for a lack of immediate efficacy if not taken on an empty stomach and therefore a potential increased risk for repeated doses, leading to overdose. The committee member who voted "Yes" stated that AVRIDI should be approved because it showed incremental improvement with its abuse deterrent properties and demonstrated efficacy when taken correctly on an empty stomach since patients would be able to adhere to the instructions with proper patient education. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 5:02 p.m. on September 10, 2015.