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
May 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 new drug application (NDA) 208653, benzhydrocodone/acetaminophen oral tablets, submitted by KemPharm, Inc., with the proposed indication of short-term (up to 14 days) management of acute pain. The product has been formulated with the intent to provide abuse-deterrent properties. Benzhydrocodone is a hydrocodone prodrug which, according to the applicant, is rapidly converted into hydrocodone by enzymes in the gastrointestinal tract. The active drugs in this fixed-dose combination are hydrocodone and acetaminophen. The applicant has submitted data to support abuse-deterrent properties for this product. The committees discussed whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling, and whether the nasal route of abuse is relevant for combination products made up of hydrocodone and acetaminophen.

These summary minutes for the May 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 May 29, 2016.

I certify that I attended the May 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/
Stephanie L. Begansky, PharmD
Designated Federal Officer, AADPAC

/s/
Raeford Brown, MD
Acting 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
May 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 May 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/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 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 May 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. The meeting was called to order by Raeford Brown, MD, FAAP (Acting 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. There were 7 Open Public Hearing (OPH) speaker presentations.

Issue: The committees were asked to discuss new drug application (NDA) 208653, benzhydrocodone/acetaminophen oral tablets, submitted by KemPharm, Inc., with the proposed indication of short-term (up to 14 days) management of acute pain. The product has been formulated with the intent to provide abuse-deterrent properties. Benzhydrocodone is a hydrocodone prodrug which, according to the applicant, is rapidly converted into hydrocodone by enzymes in the gastrointestinal tract. The active drugs in this fixed-dose combination are hydrocodone and acetaminophen. The applicant has submitted data to support abuse-deterrent properties for this product. The committees discussed whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling, and whether the nasal route of abuse is relevant for combination products made up of hydrocodone and acetaminophen.

Attendance:

Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting):
Brian T. Bateman, MD, MSc; Raeford E. Brown, Jr., MD, FAAP (Acting Chairperson); David S. Craig, PharmD; Charles W. Emala Sr., MS, MD; Anita Gupta, DO, PharmD; Jennifer G. Higgins, PhD (Consumer Representative); Abigail B. Shoben, PhD

Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting): Jeffrey L. Galinkin, MD, FAAP; Rafael V. Miguel, MD

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

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Tobias Gerhard, PhD, RPh; Jeanmarie Perrone, MD, FACMT; Marjorie Shaw Phillips, MS, RPh, FASHP; Andy S. Stergachis, PhD, RPh; Linda Tyler, PharmD, FASHP

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

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

Temporary Members (Voting): Melinda Campopiano, MD; Maureen D. Donovan, PhD; James N. Hall; Heidi Israel, PhD, FNP; Alan D. Kaye, MD, PhD; Edward Michna, MD, JD, RPh; Elaine Morrato, DrPH, MPH; Joseph O'Brien, MBA (Patient Representative)

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

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

Open Public Hearing Speakers: Julian Phillips, MBA; Bob Twillman, PhD, FAPM (American Academy of Pain Management); Shruti Kulkami (Center for Lawful Access and Abuse Deterrence); Heather McLaughlin (National Association of Drug Diversion Investigators); Michael Schatmand, PhD, CPE (US Pain Foundation); Fred Wells Brason II (Project Lazarus); Janetta Iwanicki, MD (RADARS)

The agenda was as follows:

Call to Order and Introduction of Committee	**Raeford E. Brown, Jr., MD, FAAP** Acting Chairperson, AADPAC
Conflict of Interest Statement	**Stephanie L. Begansky, PharmD** Designated Federal Officer, AADPAC
FDA Introductory Remarks	**Ellen Fields, MD** Deputy 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	**KemPharm, Inc.**
Introduction	**Travis Mickle, PhD** Chief Executive Officer KemPharm, Inc.
Clinical Perspective	**Jeffrey Gudin, MD** Director of Pain Management and Palliative Care Englewood Hospital and Medical Center Clinical Instructor, Anesthesiology Icahn School of Medicine at Mt. Sinai
Development Overview	**Travis Mickle, PhD**
Tampering Studies	**Travis Mickle, PhD**
Clinical Abuse-Deterrence Studies	**Lynn Webster, MD** Vice President, Scientific Affairs PRA Health Sciences
Post-Marketing Surveillance Future Studies	**Travis Mickle, PhD**
Benefit-Risk Profile	**Jeffrey Gudin, MD**
Clarifying Questions	
BREAK	
FDA PRESENTATIONS	
In Vitro Abuse Deterrent Studies	**Benjamin D. Stevens, PhD, MPH** Office of New Drug Products (ONDP) Office of Pharmaceutical Quality (OPQ), CDER, FDA
Results of Human Abuse Potential Studies	**James M. Tolliver, PhD** Controlled Substance Staff, CDER, FDA
Drug Utilization Patterns for Combination Hydrocodone/Acetaminophen and Other Selected Opioid Analgesics, Years 2011-2015	**Rajdeep Gill, PharmD** Division of Epidemiology II (DEPI II) Office of Pharmacovigilance and Epidemiology (OPE) Office of Surveillance and Epidemiology (OSE) CDER, FDA
Is Snorting a Relevant Route of Abuse for Hydrocodone Combination Products?	**Jana McAninch, MD, MPH, MS** DEPI II, OPE, OSE, CDER, FDA

Clarifying Questions

LUNCH

Open Public Hearing

Charge to the Committee	**Sharon Hertz, MD** Director DAAAP, ODEII, 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 the data presented for hydrocodone and acetaminophen combination drug products support that the nasal route of abuse is relevant for KP201/APAP.

   Committee Discussion: *The overall consensus of the committees was that the data presented for hydrocodone and acetaminophen drug products support that the nasal route of abuse is probably relevant for KP201/APAP, even if there is only a small relevance. The committee stated that there is some question as to whether or not the nasal route of abuse is a gateway path after the oral route that leads to other forms of abuse. It was noted that the nasal route of abuse may be more common in the adolescent population and in specific communities. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Please discuss whether there are sufficient data to support a finding that KP201 has properties that can be expected to deter abuse commenting on support for deterrent effects for each of the three possible routes of abuse:

   a. Oral
   b. Nasal
   c. Intravenous

   Committee Discussion: *The committees stated that overall they are unconvinced of the abuse deterrent properties for the nasal route of abuse as there was no compelling evidence presented. They also stated that the oral and intravenous routes of abuse are not impacted by KP201/APAP. Please see the transcript for details of the committee discussion.*

3. **VOTE:** Should KP201/APAP be approved for the proposed indication?

   Vote Result: Yes: 16 No: 4 Abstain: 0

   Committee Discussion: *The majority of the committee voted "Yes", agreeing that KP201/APAP should be approved for the proposed indication. Those members who voted "Yes" stated they support approval because of the bioequivalence data presented and since the drug product treats acute pain without evidence that it is more harmful than currently available therapies. Those who voted "No" stated that they were not persuaded by the data and couldn't promote this as a safer product compared to currently available therapies. One committee member who voted "No" noted that approving this product may have unintended consequences as they remained unconvinced that the drug product has robust deterrent properties. Please see the transcript for details of the committee discussion.*

4. **VOTE:** If approved, should KP201/APAP be labeled as an abuse-deterrent product?

   Vote Result: Yes: 2 No: 18 Abstain: 0

   Committee Discussion: *The majority of the committee voted "No", stating that KP201/APAP should not be labeled as having abuse-deterrent properties. The committee expressed concern that the data presented were not compelling to support the abuse-deterrent properties of this product and that they don't want to misguide prescribers into thinking that this may be a safer product if it is labeled and marketed as having abuse-deterrent properties. Those who voted "Yes" stated that it is an incremental improvement ("baby steps") over currently available therapies and if KP201/APAP were to be approved with abuse-deterrent labeling, it sends an important strategy message moving forward. Please see the transcript for details of the committee discussion.*

5. **DISCUSSION:** If you think the product should be approved, discuss the route or routes of abuse for which abuse-deterrent language should be included in the product label.

   Committee Discussion: *Based on the committees' discussion of questions #3 and #4, there was no need to discuss question #5. Please see the transcript for details of the committee discussion.*