Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee
December 7, 2012

Location: FDA White Oak Campus, Great Room (Rm. 1503), White Oak Conference Center, 10903 New Hampshire Ave., Silver Spring, Maryland 20993

Issue: The committee discussed the risks and benefits of new drug application (NDA) 202880, by Zogenix Inc., for hydrocodone bitartrate extended-release capsules (proposed trade name Zohydro ER), an opioid analgesic medication for the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. This formulation of hydrocodone bitartrate extended-release capsules represents the first single-entity (i.e., containing no other active pharmaceutical ingredients, such as acetaminophen or ibuprofen) hydrocodone-containing drug product. It will be formulated in dose strengths up to 50 mg, and administered twice daily (i.e., every 12 hours). The committee was asked to determine whether the benefit-risk assessment of this product favors its approval for marketing.

These summary minutes for the December 7, 2012 Anesthetic and Analgesic Drug Products Advisory Committee meeting were approved on January 4, 2013.

I certify that I attended the December 7, 2012 Anesthetic and Analgesic Drug Products Advisory Committee meeting and that these minutes accurately reflect what transpired.

_____/s/_____
Philip Bautista, PharmD
Designated Federal Officer, AADPAC

_____/s/_____
Randall P. Flick, MD, MPH
Chairperson, AADPAC

Summary Minutes of Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee
December 7, 2012

The following is the final report of the Anesthetic and Analgesic Drug Products Advisory Committee meeting held on December 7, 2012. A verbatim transcript will be available in approximately four to six weeks, sent to the Division of Anesthetic, Analgesic and Addiction Products and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm283971.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 of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 7, 2012 at the FDA White Oak Campus, Great Room (Rm. 1503), White Oak Conference Center, 10903 New Hampshire Ave., Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the background materials from the FDA and Zogenix, Inc. The meeting was called to order by Randall P. Flick, MD, MPH (Chairperson); the conflict of interest statement was read into the record by Philip Bautista, PharmD (Designated Federal Officer). There were approximately 125 people in attendance. There were seventeen (17) Open Public Hearing speakers.

Issue: The committee discussed the risks and benefits of new drug application (NDA) 202880, by Zogenix Inc., for hydrocodone bitartrate extended-release capsules (proposed trade name Zohydro ER), an opioid analgesic medication for the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. This formulation of hydrocodone bitartrate extended-release capsules represents the first single-entity (i.e., containing no other active pharmaceutical ingredients, such as acetaminophen or ibuprofen) hydrocodone-containing drug product. It will be formulated in dose strengths up to 50 mg, and administered twice daily (i.e., every 12 hours). The committee was asked to determine whether the benefit-risk assessment of this product favors its approval for marketing.

Attendance:
AADPAC Members Present (Voting): Randall P. Flick, MD, MPH (Chairperson); Vesna Jevtovic-Todorovic, MD, PhD, MBA; James G. Ramsay, MD; James H. Ware, PhD; Ursula Wesselmann, MD, PhD

AADPAC Member Present (Non-Voting): Richard L. Leff, MD (Industry Representative)

AADPAC Members Not Present (Voting): Edward C. Covington, Jr., MD; Penney Cowan (Consumer Representative); John D. Markman, MD; Anne Louise Oaklander, MD, PhD, FAAN; Knox H. Todd, MD, MPH; Cynthia Wong, MD

Temporary Members (Voting): Richard Denisco, MD, MPH; Angela Gravois (Patient Representative); Alan Kaye, MD, PhD, DABPM; Judith Kramer, MD, MS; Jane Maxwell, PhD; Rodney Mullins (Acting Consumer Representative); Jeanmarie Perrone, MD; Jack M. Rosenberg, MD; Julie Zito, PhD

FDA Participants (**Non-Voting):** Bob Rappaport, MD; Sharon Hertz MD; Ellen Fields, MD, MPH

Speaker (Non-Voting): Sharon L. Walsh, PhD

Designated Federal Officer (Non-Voting): Philip Bautista, PharmD

Open Public Hearing Speakers: Wendy Berggren Foster (US Pain Foundation); Srinivas Nalamachu, MD (Association of Chronic Pain Patients); Avi Israel (Save the Michaels of the World); Craig Beemer; Andrew Kolodny, MD (Physicians for Responsible Opioid Prescribing); Cheryl Placek; Daniel A. Busch (www.stopdrugdeath.com); Laurie Lindell (US Pain Society); Pete Jackson (Advocates for the Reform of Prescription Opioids); Jeffrey Reynolds, PhD, CEAP, SAP (Long Island Council on Alcoholism & Drug Dependence); Teri Kroll (statement read by Avi Israel); Joanna Huskey; Michael Barnes, Esq. (Center for Lawful Access and Abuse Deterrence); Bob Lund; Brandon Leonard, MA (Men's Health Network); Thomas Berger, MD (Veterans Health Council of Vietnam Veterans of America); Giselle Jackman (statement read by Andrew Kolodny, MD)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Randall P. Flick, M.D., M.P.H.** Chairperson, AADPAC
Conflict of Interest Statement	**Philip Bautista, Pharm.D.** Designated Federal Officer, AADPAC
FDA Introductory Remarks	**Bob Rappaport, MD** Director Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATIONS	**Zogenix, Inc.**
Introduction	**Stephen J. Farr, PhD** President and Chief Operating Officer Zogenix, Inc.
Medical Need for Zohydro ER	**Richard L. Rauck, MD** Pain Fellowship Doctor, Wake Forest University President, Carolinas Pain Institute President-elect, World Institute of Pain

SPONSOR PRESENTATIONS (cont.)

Zohydro ER Clinical Program Overview	**James Breitmeyer, MD, PhD** Chief Medical Officer Zogenix, Inc.
Zohydro ER Risk Evaluation and Mitigation Strategies (REMS) and Safe Use Initiatives	**Stephen J. Farr, PhD**
Benefits Risk Conclusions	**James Breitmeyer, MD, PhD**
Clarifying Questions to the Sponsor	

BREAK

FDA PRESENTATION

Outpatient Drug Utilization Patterns For Selected Opioid Analgesics in the U.S., Years 2007-2011	**Rajdeep Gill, PharmD** Drug Utilization Data Analyst Division of Epidemiology II (DEPI-II) Office of Pharmacovigilance and Epidemiology (OPE) Office of Surveillance and Epidemiology (OSE) CDER, FDA

SPEAKER PRESENTATION

Abuse Potential of Hydrocodone in Human Studies	**Sharon L. Walsh, PhD** Director Center on Drug Abuse and Alcohol Research University of Kentucky College of Medicine

FDA PRESENTATIONS

Misuse/Abuse of Hydrocodone and Oxycodone Products by Composition and Formulation: Findings from the Drug Abuse Warning Network (DAWN)	**Catherine Dormitzer, PhD, MPH** Epidemiologist DEPI-II, OPE, OSE, CDER, FDA
Extended-Release/Long-Acting Opioid Analgesics REMS: An Overview	**Robert A. Levin, MD** Medical Officer DAAAP, ODE-II, OND, CDER, FDA
Clarifying Questions to the FDA and Speaker	

LUNCH

Open Public Hearing Session	
Charge to the Committee	**Bob Rappaport, MD**

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **VOTE**: Has the Applicant demonstrated that Zohydro ER is effective for the management of moderate to severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time?

   Vote: Yes= 7 No = 6 Abstain = 1

   Committee Discussion: *The majority of the committee agreed that the Applicant demonstrated that Zohydro ER is effective for the management of moderate to severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time. The committee members who voted "Yes" stated that the Applicant had met the efficacy standards set forth by the Agency, and they agreed that the data suggest that Zohydro ER is efficacious, especially given the history of efficacy of combination hydrocodone/acetaminophen products. The committee members who voted "No" and the member who abstained agreed that the length of the 12- week study period was not sufficient to demonstrate efficacy for a chronic use indication. These committee members added that Zohydro ER only demonstrated a modest change in pain score and would not have a clinically significant impact in practice. Please see the transcript for details of the committee discussion.*

2. **VOTE**: Has the Applicant demonstrated that Zohydro ER is safe in the intended population?

   Vote: Yes= 5 No = 9 Abstain = 0

   Committee Discussion: *The committee agreed that the Applicant met the safety standards set forth by the Agency and stated that Zohydro ER is as safe as other long-acting and extended release opioid analgesics that have previously been approved. However, the majority of the committee did not agree that the Applicant demonstrated that Zohydro ER is safe in the intended population. The committee members who voted "No" shared their concerns about long-term safety risks including risk of addiction. Additionally, these committee members noted that drug diversion and deaths still occurred in clinical trials despite close monitoring, and that frequency of these adverse outcomes would likely be worse in real life clinical practice in the absence of close monitoring. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION**: Please discuss whether the data presented or discussed suggest that the postmarketing experience concerning abuse with Zohydro ER would be expected to be different from the postmarketing experience associated with other approved Schedule II extended-release opioids.

   Committee Discussion: *The committee was divided on whether the data presented or discussed suggest that the post-marketing experience concerning abuse with Zohydro ER would be expected to be different from the postmarketing experience associated with other approved Schedule II extended-release opioids. Some of the committee members thought that the post-marketing experience concerning abuse would be similar while others thought that Zohydro ER would most likely be abused more than other previously approved Schedule II extended-release opioids. Given that combination hydrocodone/acetaminophen products are the most widely abused opioid, the latter members stated that Zohydro ER would be more likely to be diverted due to the absence of acetaminophen and the lack of a tamper-resistant formulation. Please see the transcript for details of the committee discussion.*

4. **DISCUSSION**: Please discuss whether the data support the need for additional postmarketing risk mitigation requirements beyond the ER/LA REMS.

   Committee Discussion: *The committee opined that the current ER/LA Opioid Analgesic REMS will at best be modestly effective in addressing the public health issues of opioid abuse and misuse for long-acting/extended release opioid products in general.. Because the committee was not reassured of the effectiveness of the ER/LA REMS, the committee agreed that the potential for abuse of this product supports the need for additional postmarketing risk mitigation requirements beyond the current REMS. The committee stated that new requirements should include mandatory physician education, restrictive prescribing, increased surveillance, informed consent, and mandatory secure storage of opioid products by patients. The committee believed these additional risk mitigation strategies should also apply to marketed ER/LA opioids in general. Please see the transcript for details of the committee discussion.*

5. **VOTE**: Based on the data presented and discussed today, do the efficacy, safety and risk-benefit profile of Zohydro ER support the approval of this application?

   Vote: Yes= 2 No = 11 Abstain = 1

   Committee Discussion: *Although the committee agreed that the Applicant met the Agency standards for efficacy and safety, the majority of the committee did not support the approval of this application. The committee agreed that standards for opioid product approval should be raised in light of the current public health concerns of abuse and misuse. The committee stated that the FDA should not approve ER/LA opioids without tamper-resistant or abuse-deterrent formulations, and that additional risk mitigation features should be adopted to strengthen the current ER/LA Opioid Analgesic REMS. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:47 p.m.