Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee Meeting
June 11-12, 2014

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

Topic: The committee discussed the potential cardiovascular risk associated with products in the class of peripherally-acting opioid receptor antagonists and the necessity, timing, design and size of cardiovascular outcomes trials to support approval of products in the class for the proposed indication of opioid-induced constipation in patients taking opioids for chronic pain.

These summary minutes for the June 11-12, 2014, meeting of the Anesthetic and Analgesic Drug Products Advisory Committee of the Food and Drug Administration were approved on July 28, 2014.

I certify that I attended the June 11-12, 2014, 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/ Randall Flick, MD, MPH
Chairperson, AADPAC
The following is the final report of the Anesthetic and Analgesic Drug Products Advisory Committee meeting held on June 11-12, 2014. A verbatim transcript will be available in approximately six weeks, sent to the Division of Analgesia, Anesthesia and Addiction Products and Division of Gastroenterology and Inborn Errors Products and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm390304.htm.

All external requests for the meeting transcripts 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 June 11 and 12, 2014, at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Industry (AstraZeneca, Cubist, Develco, Salix, and Theravance). The meeting was called to order by Randall Flick, MD (Chairperson). The conflict of interest statement was read into the record by Stephanie Begansky, PharmD (Designated Federal Officer). There were approximately 200 people in attendance each day. There were no Open Public Hearing (OPH) speaker presentations.

**Issue:** The committee discussed the potential cardiovascular risk associated with products in the class of peripherally-acting opioid receptor antagonists and the necessity, timing, design and size of cardiovascular outcomes trials to support approval of products in the class for the proposed indication of opioid-induced constipation in patients taking opioids for chronic pain.

**Attendance:**

**Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting):**
Randall P. Flick, MD, MPH (Chairperson); Charles W. Emala Sr., MS, MD; Jennifer G. Higgins, PhD, CCRP (Consumer Representative); Alan D. Kaye, MD, PhD; Cynthia Wong, MD

**Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting):**
David S. Craig, PharmD; Rafael V. Miguel, MD; Gary A. Walco, PhD; James H. Ware, PhD; Ursula Wesselmann, MD, PhD

**Anesthetic and Analgesic Drug Products Advisory Committee Member Not Present (Non-Voting):**
Richard L. Leff, MD (Industry Representative)

**Temporary Members (Voting):**
Brian T. Bateman, MD, MSc; Mitchell S. Cappell, MD, PhD; Brendan M. Everett, MD, MPH; Linda A. Feagins, MD; Tobias Gerhard, PhD, RPh; Sonia Hernandez-Diaz, MD, DrPH; Vesna Jevtovic-Todorovic, MD, PhD; Marvin A. Konstam, MD;
The agenda was as follows:

**Day 1: Wednesday, June 10, 2014**

- **Call to Order and Introduction of Committee**
  - Randall P. Flick, MD, MPH
  - Chairperson, AADPAC

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

- **Cardiovascular Assessment of Peripherally Active Mu-Opioid Antagonists**
  - Donna Griebel, MD
  - Director
  - Division of Gastroenterology and Inborn Errors Products (DGIEP)
  - Office of Drug Evaluation III (ODE III)
  - Office of New Drugs (OND), CDER, FDA

**Guest Speaker Presentation**

- **Role of Peripheral Mechanisms in Opioid Pharmacology**
  - Gavril Pasternack, MD, PhD
  - Anne Burnett Tandy Chair in Neurology and Laboratory Head, Molecular Pharmacology and Chemistry
  - Memorial Sloan-Kettering Cancer Center

**Clarifying Questions**

**Break**

**Industry Presentation - Collaborative**

**Clarifying Questions**

**Industry Presentations**

- **Alvimopan - Retrospective Evaluation of Opioid Withdrawal and Cardiovascular Safety With Long-term Use in Opioid-induced Constipation**
  - Jennifer Liscouski
  - Director, Regulatory Affairs
  - Cubist Pharmaceuticals, Inc.
INDUSTRY PRESENTATIONS (CON’T)

Kate Lane, PhD, DABT
Director, Regulatory Nonclinical
Cubist Pharmaceuticals, Inc.

Lee Techner, DPM
Vice President, Clinical Research
Cubist Pharmaceuticals, Inc.

Clarifying Questions

LUNCH

INDUSTRY PRESENTATIONS

Salix Pharmaceuticals, Inc.

Introduction

William P. Forbes, PharmD
Executive Vice President
Medical, Research & Development and Chief
Development Officer

Clinical Pharmacology

Pamela Golden, PhD
Associate Vice President
Nonclinical and Clinical Pharmacology

Clinical Review of Safety

Craig Paterson, MD
Vice President
Medical and Clinical Development

Summary

William P. Forbes, PharmD
Executive Vice President
Medical, Research & Development and Chief
Development Officer

Clarifying Questions

INDUSTRY PRESENTATIONS

AstraZeneca

MOVANTIK™ NDA

William Mezzanotte, MD, MPH

Overview of MOVANTIK Efficacy and Safety in
the Clinical Development Program

Mark Sostek, MD

Cardiovascular Safety of MOVANTIK

William B. White, MD

Clarifying Questions

BREAK

INDUSTRY PRESENTATION

Theravance, Inc.
Preclinical Properties of Axelopran  
David Beattie, PhD  
Pharmacology  
Theravance, Inc.

Clarifying Questions

INDUSTRY PRESENTATIONS

Develco Pharma Schweiz AG

Introduction

Dr. Nils Burger  
Head Clinical Project Management  
Develco Pharma Schweiz AG

Oral Naloxone Pharmacology and Pharmacokinetics

Georg Petroianu, MD, PhD, FCP  
Professor and Chair  
Cellular Biology and Pharmacology  
Associate Dean for Clinical Research  
Florida International University  
Herbert Wertheim College of Medicine

Oral Naloxone Clinical and Pharmacovigilance Overview

Mori Krantz, MD  
Cardiology Division, Denver Health  
Professor of Medicine  
University of Colorado Denver

Clarifying Questions

INDUSTRY PRESENTATION – COLLABORATIVE

FDA PRESENTATION

End of Day 1 Summary

Robert P. Fiorentino, MD, MPH  
Medical Team Leader  
DGIEP, ODE III, OND, CDER, FDA

Clarifying Questions

ADJOURNMENT

Day 2: Thursday, June 12, 2014

Call to Order and Introduction of Committee

Randall P. Flick, MD, MPH  
Chair, AADPAC

Conflict of Interest Statement

Stephanie L. Begansky, PharmD  
Designated Federal Officer, AADPAC

INDUSTRY PRESENTATION - COLLABORATIVE

FDA PRESENTATIONS

Post-marketing Risk Assessment Tools for  
Sukhminder K. Sandhu, PhD, MPH, MS
Questions to Committee/Committee Discussion

1. **DISCUSSION:** Discuss whether the totality of data suggests a cardiovascular safety signal associated with the use of peripherally active mu opioid receptor antagonists. Include in your discussion:
   a. the strength of the signal
   b. whether you believe the signal is limited to a certain drug(s) within the class or whether you believe there is a class effect
   c. the biologic plausibility of the signal:
      i. the effect of opioid withdrawal on the autonomic nervous system and the relevance of hemodynamic changes on risk of cardiovascular events
      ii. the effect of off-target receptor affinity for opioid receptors on the heart
      iii. other effect(s)

   **Committee Discussion:** There was a split in the committee members’ view of whether the totality of the data suggests a cardiovascular safety signal associated with the use of peripherally active mu opioid receptor antagonists (PAMORAs). Among the committee members that did believe there was a signal, the consensus was that it was a weak signal but not ignorable; their concerns were primarily driven by the Entereg 12-month controlled trial. They advised that whatever studies are requested should be commensurate with the weakness of the signal. Others did not believe there was a cardiovascular safety signal with any member of the class. There was a general consensus that the available data were insufficient to implicate specific biologic mechanisms for the signal. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Discuss the feasibility of conducting a cardiovascular outcomes trial in patients with chronic non-cancer pain who have opioid-induced constipation, in which patients are randomized to the peripherally active mu opioid receptor antagonist or placebo, as
add-on to background therapy. As part of this discussion, consider what would be an acceptable degree of risk that would need to be excluded in such a trial.

Committee Discussion: The consensus of the committee was that while conducting a cardiovascular outcomes trial is feasible, there are a variety of challenges including, but not limited to, anticipated high dropout rates, and the large sample sizes that would be required to study a population that is not enriched with patients at higher cardiovascular risk. Additionally, the committee recommended that a compressed time frame may eliminate some of the challenges. A few panel members considered a 2-fold increase in risk as an acceptable degree of risk that would need to be excluded in such a trial. Please see the transcript for details of the committee discussion.

3. VOTE: Should FDA require cardiovascular outcomes trials for peripherally active mu opioid receptor antagonists being developed for the treatment of opioid-induced constipation in patients with chronic, non-cancer pain?

   A. Yes, for all peripherally active mu opioid receptor antagonists
   B. Yes, but only for specific peripherally active mu opioid antagonists.
   C. No.

Discuss your answer. If you choose option “B”, please specify which specific mu opioid antagonists should be required to conduct a cardiovascular outcome trial and what concerns form the basis for such a requirement.

\[A=7\quad B=5\quad C=12\quad Abstain=0\]

Committee Discussion: A number of panel members stated they felt the question implied all alternative trial design, such as observational studies, rather than randomized controlled clinical trials. Thus five members verbally changed their answer to “C” which occurred during the committee discussion and is not reflected in the voting results above. The majority of the panel members stated that they wanted to see an observational study conducted, not a randomized controlled clinical trial. However, of the seven panel members who stated that they did in fact intend to choose “A” or “B”, the majority stated that they would like to see some kind of controlled clinical trials for Entereg. Two stated that the controlled clinical trial for Entereg would not necessarily have to be a dedicated cardiovascular outcome trial, i.e, limited to repeating the trial in which the signal was observed.

4. DISCUSSION: If a cardiovascular outcomes trial is required for a peripherally active mu opioid receptor antagonist being developed for the treatment of opioid-induced constipation in patients with chronic, non-cancer pain, discuss whether the trial should be required in the pre-approval setting, required in the post-marketing setting, or in a combination of pre-approval and post-marketing settings.

Committee Discussion: Question 4 and 5 were discussed together and are summarized below under Question 5.

5. DISCUSSION: If a cardiovascular outcomes trial is not required, discuss whether a longer term controlled clinical trial should be required pre-approval to further assess the safety of peripherally active mu opioid receptor antagonists being developed for the chronic treatment
of opioid-induced constipation in patients with non-cancer pain. Describe specific outcomes
that should be assessed in such a trial and the appropriate duration of the trial.

Committee Discussion: The consensus of the committee was that for products in
development, pre-approval general safety trials should be of sufficient duration to assess
long term outcomes (e.g., 12 months). In addition, the committee stated that post-marketing
observational studies may also be conducted (post-approval) and that appropriate measures
should be taken to enrich them with high cardiovascular risk patients. One member stated
that post-marketing observational studies using the Mini-sentinel and Medicare databases
may be used. Some members stated that a self-controlled study design may be an option.
Please see the transcript for details of the committee discussion.

On Day 1, June 11, 2014, the meeting was adjourned at approximately 4:33 p.m.
On Day 2, June 12, 2014, the meeting was adjourned at approximately 1:00 p.m.