

## **Final Minutes**

### **Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee**

**November 14, 2008**

A verbatim transcript will be available in approximately four to six weeks, sent to the Division and posted on the FDA website at: <http://www.fda.gov/ohrms/dockets/ac/cder08.html#AnestheticLifeSupport>

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

Prior to the meeting, the members and the invited consultants were provided the background material from the FDA and sponsor. The meeting was called to order by Jeffrey R. Kirsch, M.D. (Acting Chair, ALSDAC); the conflict of interest statement was read into the record by Kalyani Bhatt (Designated Federal Official). There were approximately 150 persons in attendance. There were 11 speakers for the Open Public Hearing Session

#### **Attendance:**

##### **Anesthetic and Life Support Drugs Advisory Committee Members Present (voting)**

Jeffrey R. Kirsch, MD, Nancy Nussmeier, MD, Julia Pollock, MD, Athena F. Zuppa, MD, Daniel Zelterman, MD,

##### **Drug Safety and Risk Management Advisory Committee Members Present (voting)**

Timothy Lesar, PharmD., Sean Hennessy, PharmD, PhD, Sidney Wolfe, MD, Judith Kramer, MD, MS

##### **Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Consultants (voting):**

Sorin Brull, MD, Richard Denisco, MD, Harriet de Wit, PhD, Robert Kerns, MD, Susan Krivacic (Patient Representative), Karl Lorenz, MD, Leonard Paulozzi, MD, MPH, Jack Rosenberg, MD, Sidney Wolfe, MD (Consumer Representative), Michael Yesenko (Patient Representative)

##### **Industry Representative for the Anesthetic and Life Support Drugs Advisory Committee (non-voting):** Bartholomew Tortella, MD MTS, MBA

##### **Anesthetic and Life Support Drugs Advisory Committee Members Absent:**

David G. Nichols, MD, MBA, John T. Farrar, MD

##### **Drug Safety and Risk Management Advisory Committee Members Absent:**

Terry C. Davis, PhD, Sander Greenland, Dr., P.H., Susan Heckbert, MD, PhD

**Open Public Hearing Speakers:**

- Ray Albert- Pain Medicine Solutions
- Cameron Muir –Medical Services Solution
- Micke Brown-American Pain Foundation
- Frederick Burgess-American Academy of Pain Medicine
- Phyllis Zimmer - Nurse Practitioner Healthcare Foundation
- Charles F. Cicchon-National Association of Drug Diversion
- Lance Merrill-Dads Against Drug Dealer
- Gwenn Herman-Chronic Pain Out Reach Center, Inc
- James Broatch-Reflex Sympathetic Dystrophy Syndrome Association
- Katherine Walker-University of Maryland School of Pharmacy
- Lenore Duensing-American Pain Foundation, American Academy of Pain Medicine

**AGENDA**

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*The committees will discuss new drug application (NDA) 22-321, EMBEDA (morphine sulfate extended-release with sequestered naltrexone hydrochloride) Capsules, Alpharma Pharmaceuticals L.L.C., and its safety for the proposed indication of management of moderate to severe chronic pain. The naltrexone component of this formulation is intended to mitigate abuse of the product when attempts are made to defeat the controlled-release properties of the formulation.*

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| Call to Order<br>Introduction of Committee        | <b>Jeffrey R. Kirsch, M.D.</b><br>Acting Chair, ALSDAC  |
| Conflict of Interest Statement                    | <b>Kalyani Bhatt, M.S.</b><br>Designated Federal Officer, ALSDAC  |
| Opening Remarks                                   | <b>Bob A. Rappaport, M.D.</b><br>Director, Division of Anesthesia, Analgesia,<br>Rheumatology Products CDER/FDA   |
| <b>Sponsor Presentations</b>                      | <b>Alpharma Pharmaceuticals, LLC</b>  |
| Opening Remarks                                   | <b>Joseph Stauffer, D.O.</b><br>Chief Medical Officer, Senior Vice President<br>Clinical Research & Medical Affairs<br>Alpharma Pharmaceuticals LLC<br>Assistant Professor<br>Johns Hopkins University, School of Medicine<br>Department of Anesthesiology and Critical Care<br>Division of Pain Medicine |
| Defining the Prescription Opioid Abuse<br>Problem | <b>Nathaniel Katz, M.D., M.S.</b><br>President, Analgesic Research<br>Adjunct Assistant Professor, Tufts University School<br>of Medicine and Public Health   |

Formulation Development Program

**William Vincek, Ph.D.**

Senior Vice President  
Research & Development & Regulatory Affairs  
Alpharma Pharmaceuticals LLC

Summary of Clinical Data

**Donald Manning, M.D., Ph.D.**

Vice President of Clinical Research and Development  
Alpharma Pharmaceuticals LLC  
Clinical Associate Professor  
Anesthesiology and Pain Management  
University of Virginia Health System

Abuse-Liability Studies

**Sandra D. Comer, Ph.D.**

Associate Professor of Clinical Neurobiology  
Division on Substance Abuse  
Department of Psychiatry  
Columbia University & the  
New York State Psychiatric Institute

Risk Management Program, REMS &  
Closing Remarks

**Joseph Stauffer, D.O.**

Chief Medical Officer, Senior Vice President  
Clinical Research & Medical Affairs  
Alpharma Pharmaceuticals LLC  
Assistant Professor  
Johns Hopkins University, School of Medicine  
Department of Anesthesiology and Critical Care  
Division of Pain Medicine

## **FDA Presentations**

FDA Perspective on ALO-01 Studies

**Srikanth C. Nallani, Ph.D.**  
Senior Clinical Pharmacologist  
Office of Clinical Pharmacology  
CDER/FDA

History of Modified-Release Morphine  
And Opioid/Antagonist Combinations

**Ellen Fields, M.D.**  
Lead Medical Officer,  
Division of Anesthesia, Analgesia, &

Rheumatology Products CDER/FDA

Outpatient Drug Utilization Trends  
for Morphine Products

**Laura Governale, Pharm.D., M.B.A.**  
Drug Utilization Analyst Team Leader  
Division of Epidemiology  
Office of Surveillance and  
Epidemiology  
(OSE), CDER/FDA

Summary of Drug Abuse Rates in the US:  
Morphine

**Cathy Dormitzer, Ph.D., M.P.H.**  
Division of Epidemiology  
OSE/CDER/FDA

Questions to the presenters

Open Public Hearing

Discussion and Questions to the Committee

**FOOD AND DRUG ADMINISTRATION**  
Center for Drug Evaluation and Research

*Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety & Risk Management Advisory Committee*

**QUESTIONS to the COMMITTEE**

**November 14, 2008**

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*NDA 22-321, EMBEDA (morphine sulfate extended-release with sequestered naltrexone hydrochloride) Capsules, Alpharma Pharmaceuticals L.L.C., for the proposed indication of management of moderate to severe chronic pain. The naltrexone component of this formulation is intended to mitigate abuse of the product when attempts are made to defeat the controlled-release properties of the formulation.*

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***All questions were for Committee Discussion only; no votes were taken.***

1. a. Discuss the adequacy of the tools we have to assess the impact of a novel opioid formulation on abuse, misuse and diversion of the product in the community.

*The general consensus was the necessity of monitoring Risk Evaluation and Mitigation Strategies (REMS) outcomes for patients with serious chronic pain as well as understanding their effects on diversion.*

*The committee indicated that the REMS should be evidence-based.*

*The committee felt that there should be one standard set of tools that sponsors would be expected to employ in order to assess the abusibility and surveying the abusibility of the product.*

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- b. Discuss whether or not the available data suggest that this formulation will be less susceptible to abuse and misuse.

*The committee felt that the available data suggested that the current formulation is less susceptible to abuse and misuse by the oral route of administration. The committee expressed concern that this new formulation would not prevent easy extraction of an intravenous preparation that would exclude naltrexone.*

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2. Many of the cases of addiction, overdose and death are associated with abuse of intact controlled-release opioid products. EMBEDA is formulated to release naltrexone only following physical manipulation.

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- a. Discuss whether inclusion of data on the release characteristics of the naltrexone in this new formulation into the product labeling could potentially

mislead prescribers or patients into thinking that this new formulation, when taken as directed, is less likely to be addictive, or unlikely to be abused or result in addiction or overdose.

b. If you believe that patients or prescribers could be misled, discuss whether this risk is acceptable, considering the potential benefits of the changes to the formulation.

The answers to a & b:

*The committee felt that it would be appropriate if the caution section of labeling defined the possibility of withdrawal symptoms developing or lack of efficacy after crushing, due to the release of naltrexone. Usual cautions regarding dosing should also be stated in the labeling. The committee was not in support of any statement that would suggest that this formulation or REMS will reduce the risk of abuse.*

Clarification:

*The agency stated no one will be receiving claims of reduce of liability until they prove that claim.*

3. a. If, from Question 1, you believe that the data suggest that this formulation of controlled-release morphine is likely to reduce its abuse and misuse, discuss whether or not any of the data should be included in the product labeling.

*The committee felt it was important to include the data regarding the inclusion of naltrexone center and release of crushing or chewing, which is an obvious mild deterrent to a common form of abuse. It would be good for the clinician, abusers and patients to know about this information.*

- b. If so, which specific data do you think should be incorporated into the labeling?

*The committee felt they already answered this question.*

*The meeting adjourned at approximately 4:00 p.m.*