Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
Joint Meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees

May 6, 2008
Holiday Inn, Gaithersburg
Two Montgomery Village Avenue, Gaithersburg, MD.

Anesthetic and Life Support Drugs Advisory Committee Members Present (voting)
Kanwaljeet J.S. Anand, M.D., Ph.D., Jeffrey R. Kirsch, M.D., Nancy Nussmeier, M.D., Donald S. Prough, M.D., Athena F. Zuppa, M.D.

Drug Safety and Risk Management Advisory Committee Members Present (voting)
Timothy Lesar, Pharm.D.

Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Consultants (voting):
Diane Aronson, B.S. (Acting Consumer Representative), Warren K. Bickel, Ph.D., Charles R. Cortinovis, M.D. Ruth S. Day, Ph.D., Jacqueline Gardner, Ph.D., Thomas Kosten, M.D., Susan Krivacic (Patient Representative), Jane C. Maxwell, Ph.D., Lewis S. Nelson, M.D., Leonard Paulozzi, M.D., M.P.H., Sulpicio de Guzman Soriano, III, M.D., Frank Vocci, Ph.D., Sidney Wolfe, M.D. (Acting Consumer Representative), Michael Yesenko (Patient Representative)

Industry Representative (non-voting):
Charles McLeskey, M.D.

Anesthetic and Life Support Drugs Advisory Committee Members Absent:
David G. Nichols, M.D., M.B.A., John T. Farrar, M.D.

Drug Safety and Risk Management Advisory Committee Members Absent:
Terry C. Davis, Ph.D., Sander Greenland, Dr.P.H., Susan Heckbert, M.D., Ph.D., Sean Hennessy, PharmD, Ph.D., Judith M. Kramer, M.D., M.S., Richard Platt, M.D., M.Sc.

GUEST SPEAKER *(non-voting)*
Judy K. Ball, Ph.D., M.P.A.

FDA Participants:
Douglas Throckmorton, M.D., Curtis Rosebraugh, M.D., Bob Rappaport, M.D., Henry Francis, M.D., Sharon Hertz, M.D.

Open Public Hearing Speakers:
John Markman, Andrea Cooper, Art VanZee, Jennifer Bolen, James Broatch, Melissa Zuppardi, Kristen Thacker and David Larson

Executive Secretary
Teresa A. Watkins

I certify that I attended the May 6, 2008 meeting of the Drug Safety and Risk Management Advisory Committee and that these minutes accurately reflect what transpired.

_____-s-_____
Teresa A. Watkins
Executive Secretary, DSaRM

_____-s-_____
Sulpicio de Guzman Soriano, III, M.D.
Acting Chair, ALSDAC

Minutes
Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee
May 6, 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. The meeting was called to order by Sulpicio de Guzman Soriano, III, M.D. (Acting Chair, ALSDAC); the conflict of interest statement was read into the record by Teresa Watkins (Acting Designated Federal Official). There were approximately 225 persons in attendance. There were 8 speakers for the Open Public Hearing Session

Attendance:

Anesthetic and Life Support Drugs Advisory Committee Members Present (voting)
Kanwaljeet J.S. Anand, M.D., Ph.D., Jeffrey R. Kirsch, M.D., Nancy Nussmeier, M.D., Donald S. Prough, M.D., Athena F. Zuppa, M.D.

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Industry Representative (non-voting):
Charles McLeskey, M.D.

Anesthetic and Life Support Drugs Advisory Committee Members Absent:
David G. Nichols, M.D., M.B.A., John T. Farrar, M.D.

Drug Safety and Risk Management Advisory Committee Members Absent:
Terry C. Davis, Ph.D., Sander Greenland, Dr.P.H., Susan Heckbert, M.D., Ph.D., Sean Hennessy, PharmD, Ph.D., Judith M. Kramer, M.D., M.S., Richard Platt, M.D., M.Sc.

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Issue:
The committee will discuss supplemental new drug application (sNDA) 21-947/s-005, FENTORA (fentanyl buccal tablet), Cephalon, Inc., and its safety for the proposed indication of breakthrough pain in opioid tolerant non-cancer patients with chronic pain

The agenda proceeded as follows:

Call to Order	**Sulpicio de Guzman Soriano, III, M.D.** Acting Chair, ALSDAC
Introduction of Committee	
Conflict of Interest Statement	**Teresa Watkins, Pharm.D., R.Ph.** Acting Designated Federal Officer, ALSDAC/DSaRM
Opening Remarks	**Bob Rappaport, M.D.** Director, Division of Analgesia, Anesthesia, and Rheumatology Products (DAARP), CDER/FDA
Sponsor Presentation	Cephalon
Introduction and Closing	**Eric Floyd, M.S., M.B.A., Ph.D.** Vice President, Regulatory Affairs Cephalon, Inc.
Medical Need/Overview of Breakthrough Pain(BTP)	**Perry G. Fine, M.D.** Professor of Anesthesiology The University of Utah School of Medicine
Efficacy, Landscape, and Perceived Risks	**John Messina, PharmD** Senior Director, Clinical Research Cephalon, Inc.

Safety and Risk Management	**Juergen Schmider, M.D., Ph.D.** Corporate Safety Officer and Vice President, Global Pharmacovigilance and Epidemiology Cephalon, Inc.
Closing Remarks	Lesley Russell, MBChB, M.R.C.P.
Background on Transmucosal Fentanyl Products	**Ellen Fields, M.D., M.P.H.** Clinical Team Leader, DAARP, CDER/FDA
Actiq and Fentora Drug Utilization Trends	**LCDR Kendra Worthy, Pharm.D.** U.S. Public Health Service Commissioned Corps Drug Utilization Analyst Division of Epidemiology Office of Surveillance and Epidemiology (OSE), CDER/FDA
Break	
Review of Fentora and Actiq Adverse Events from the Adverse Event Reporting System (AERS) Database	**Yoo Jung Chang, Pharm.D.** Safety Evaluator Division of Adverse Event Analysis II, OSE, CDER/FDA
FENTORA Medication Errors	**LCDR Kristina C. Arnwine, PharmD** Acting Team Leader Division of Medication Error Prevention OSE, CDER/FDA
Fentora Abuse Potential in the Noncancer Population	**Lori A. Love, M.D., Ph.D**. Medical Officer Controlled Substance Staff (CSS), CDER/FDA
Findings from the Drug Abuse Warning Network (DAWN)	**Judy K. Ball, Ph.D., M.P.A.** Director, Division of Operations Office of Applied Studies Substance Abuse and Mental Health Services Administration, DHHS
FDA Safety Analysis of Supplement 005	**Robert Shibuya, M.D.** Medical Officer,

DAARP, CDER/FDA

Fentora Risk Management: Postmarketing Experience and Recommendations

Jeanine Best, M.S.N.,R.N.,P.N.P.
Senior Drug Risk Management Analyst
Division of Risk Management
OSE, CDER/FDA

Questions for Presenters

Lunch

Open Public Hearing

Discussion/Questions to the Committee(Vote)

Questions to the Committee:

1. Do breakthrough pain episodes experienced by patients with chronic pain that is not related to cancer usually require treatment with potent opioids such as fentanyl, or can they be adequately managed with less potent opioid or non-opioid analgesics?

   -Many felt that for some special groups of patients with non-cancer related chronic pain that treatment of breakthrough pain needs to be treated with potent opioids, but that they did not feel it applied to all patients with non-cancer related breakthrough pain.
   -Some felt that alternatives to opioids, both pharmacologic and behavioral approaches, need to be further studied.
   -Many felt that the sponsor needs to compare fentanyl to other lesser opioids and non-opioid therapies, rather than against placebo to establish a difference over the existing therapies.
   -Others felt they needed more information to make the determination.

2. Can Fentora be prescribed to a broad, non-cancer, opioid-tolerant patient population cared for by a variety of specialists and primary care physicians, without a significant increase in morbidity and mortality related to misprescribing and misuse of the product?

   Although a formal vote was not taken, the consensus of the committee was no.
   Most felt that they would like to see the sponsor's proposed risk management plan implemented for the currently approved indication; and that data be collected to show that it does, indeed, reduce off-label prescribing, prior to broadening the indication to patients with non-cancer related chronic pain.

3. Fentora has attributes that make it particularly attractive to abusers and attributes that make it particularly dangerous for those who do abuse it. In light of the increasing abuse of prescription opioids and the specific attributes of this particular product, would the widely increased availability of Fentora likely lead to widespread abuse and the public health consequences of that abuse?

   -The committee requested abuse liability data from the sponsor's consultant. That consultant stated that there was no difference in abuse liability between fentanyl and oxycodone or heroin.
   -Some expressed concern that expanded availability could correlate to increased abuse.
   -Many were concerned with diversion of the product to and use by non-opioid tolerant individuals leading to the very real possibility of deaths.
   -There is concern that the trends show that opioid abuse is greater in younger age groups (ages 18-25) than others and that the new indication would encompass many more younger patients. This could result in increased abuse.
   -There is concern that, in the clinical trials conducted by the sponsor, any patient with any tendency toward abuse was excluded, yet at least 1 in 20 of the patients remaining in the trial who were deemed not at risk for abuse, did indeed, abuse the product.

4. If there is a substantial risk for increased abuse of this product due to greater availability, can this risk be effectively managed; and, if so, what specific risk management tools would be necessary to mitigate this risk while still ensuring reasonable access for patients who meet the conditions of labeling?

   -Members requested that the sponsor make sure the Risk Management plan is well thought out and that it be able to be completely implemented on Day 1 of marketing.
   -They wanted to bring to the sponsor's attention the difficulty that placing "hardstops" in a risk management plan would pose to pharmacists.
   -They want a proactive plan by the company to "buy back" unused Fentora so that it does not remain in medicine cabinets when no longer needed and pose a greater risk for diversion or abuse.
   -Many want the proposed Risk Management Plan applied to the currently approved indication first, and then to the proposed new indication.
   -However, they want compassionate use authorized.
   -The committee likes the sponsor's proposed outpatient Risk Management Plan, however, feels that an inpatient Risk Management Plan is also needed.

5. Considering your responses to the earlier questions, do you recommend approval of the expansion of the indication for Fentora to opioid-tolerant, non-cancer, chronic pain patients with breakthrough pain? **Please vote yes or no**.

   YES = 3
   NO = 17
   ABSTAIN = 0
   TOTAL = 20

   - If you voted yes, what means to mitigate abuse and diversion should FDA consider requiring? Do you recommend additional studies?

     Implement the proposed Risk Management Plan for the current indication, collect data to show that it actually reduces off-label prescribing, misuse and abuse of the product prior to expanding the indication to patients with non-cancer related chronic pain.

   - If you voted no, are there additional studies that the sponsor should conduct to address the reasons you think the drug should not be approved?

     -Most suggested clinical efficacy comparator trials.
     -Many wanted to have the Risk Management Plan implemented and assessed for effectiveness, along with a report on the outcomes.
     -Some recommended introducing public health initiatives and outreach that target youth (e.g., public service awareness ad campaigns) to address the false sense of security that they tend to have about prescription drugs being safer to abuse than illicit/illegal drugs.
     -Others felt that prescribing of fentanyl should be restricted primarily to pain management clinics who utilize protocol prescribing to decrease diversion.

4:15 p.m. Adjourn