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Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and Drug Safety and Risk Management Advisory Committee (DSaRM) Hilton Washington DC North/Gaithersburg, The Ballrooms, 620 Perry Parkway, Gaithersburg, Maryland. April 22, 2010

Summary Minutes

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

These summary minutes for the April 22, 2010 Meeting of the Joint Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committee Meeting of the Food and Drug Administration were approved on April 28, 2010.

I certify that I attended the April 22, 2010 meeting of the Joint Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committee Meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	/s/_
Kalyani Bhatt	Jeffrey R. Kirsch, M.D.
Designated Federal Official, ALSDAC	Chair

Summary Minutes

Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee April 22, 2010

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. (Chair, ALSDAC); the conflict of interest statement was read into the record by Kalyani Bhatt (Designated Federal Official). There were approximately 100 persons in attendance. There were 18 speakers for the Open Public Hearing session.

Attendance:

Anesthetic and Life Support Drugs Advisory Committee Members Present (voting): Edward Covington, M.D., Randall Flick, M.D., Jeffrey R. Kirsch, M.D. (Chair), Daniel Zelterman, M.D.,

Industry Representative Member for the Anesthetic and Life Support Drugs Advisory Committee Present (non-voting):

Bartholomew Tortella, M.D., M.T.S, M.B.A.

Drug Safety and Risk Management Advisory Committee Members Present (voting): Elaine Morrato, Dr.P.H., M.P.H., C.P.H., Lewis Nelson, M.D.; Allen J. Vaida, Pharm.D, FASHP, Sidney Wolfe, M.D. (Consumer Representative)

Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Consultants Present (Temporary Voting Members):

Ann Berger, MSN, M.D., Charles Cleeland, M.D., Barbara Insley Crouch, Pharm.D., M.S.P.H., DABAT, Harriet de Wit, Ph.D., Robert Dubbs, J.D., M.B.A. (Patient Representative), John T. Farrar, M.D., Ph.D., Robert Kerns, Ph.D., Maria E. Suarez-Almazor, M.D., Ph.D., Dennis C. Turk, Ph.D., Gary Walco, M.D., Almut G. Winterstein, Ph.D., Michael L. Yesenko, M.D., (Patient Representative)

Anesthetic and Life Support Drugs Advisory Committee Members Absent: Sorin J. Brull, M.D., Jayant K. Deshpande, M.D., John Markman, M.D., Knox Todd, M.D., Osemwota A. Omoigui, M.D., Robert K. Stoelting, M.D., Athena Zuppa, M.D. (cancelled attendance day of meeting)

Drug Safety and Risk Management Advisory Committee Members Absent: D. Bruce Burlington, M.D. (Industry Representative), Sander Greenland, Dr.PH., Susan Heckbert, M.D., Ph.D., Judith M. Kramer, M.D. M.S.

Summary Minutes

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Open Public Speakers:

- 1. George E. Downs, Pharm.D. (Professor and Dean Emeritus, Philadelphia College of Pharmacy University of the Sciences in Philadelphia)
- 2. John Nosack (Center for Lawful Access and Abuse Deterrence)
- 3. David Williams (National Family Partnership)
- 4. Michelle Lipinski, Director (Northshore Recovery High School)
- 5. Alyssa Dedrick (Northshore Recovery High School)
- 6. Dena Bowers (Northshore Recovery High School)
- 7. Michael Provenchur (Northshore Recovery High School)
- 8. Katherine E. Galluzzi, D.O., FACOFP (Professor and Chairperson Department of Geriatrics, Philadelphia College of Osteopathic Medicine)
- 9. Steven H Steiner (Founder of DAMMAD, Dads and Mad Moms Against Drug Dealers)
- 10. Phyllis Zimmer (President of the Nurse Practitioner Healthcare Foundation)
- 11. Paul Brown (President, National Research Center for Women & Families)
- 12. Charlie Cichon, Executive Director, National Association of Drug Diversion Investigators (NADDI)
- 13. Nicole Jasper, M.D. (Emergency Medicine Physician)
- 14. Lennie Duensing, Med (Executive Director, American Academy of Pain Management)
- 15. Mary Lynn McPherson, Pharm.D., BCPS, CPE (Professor and Vice Chair Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy)
- 16. Mary Bennett, MFA (Director of Grassroots Advocacy American Pain Foundation)
- 17. Teresa Shaffer (Advocate for people with pain)
- 18. Deana Luchs (Advocate for people with pain)

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

AGENDA

April 22, 2010

Agenda: The committees will discuss new drug application (NDA) 22-451 ACUROX (oxycodone HCl and niacin) Tablets, Acura Pharmaceuticals, Inc., for the proposed indication of relief of moderate to severe pain where the use of an immediate-release, orally administered, opioid analgesic tablet is appropriate, and the results of studies evaluating the addition of niacin, added for the purpose of reducing the misuse of oxycodone.

Call to Order Jeffery Kirsch, MD
Introduction of Committee Chair, ALSDAC

Conflict of Interest Statement Kalvani Bhatt

Designated Federal Official, ALSDAC

Opening Remarks Robert Shibuya, MD

Clinical Team Leader, Division of Anesthesia and Analgesia Products CDER/FDA

History of "abuse-deterrent" combination Frank Pucino, PharmD, opioids MPH

Clinical Reviewer Division of Anesthesia and Analgesia Products CDER/FDA

Sponsor Presentations

Introduction Eric G. Carter, PhD, MD

Chief Science Officer King Pharmaceuticals, Inc.

Acurox Tablets Clinical Development ProgramFocus on Niacin

Kenneth Sommerville, MD,
FAAN

Vice President, Clinical

Development

King Pharmaceuticals, Inc. Adjunct Assistant Professor of Medicine Duke University

Acurox Tablets Abuse Liability Clinical Studies

Lynn R. Webster, MD, FACPM, FASAM Medical Director Lifetree Clinical Research and Pain Clinic

Concluding Remarks

Eric G. Carter, PhD, MD

FDA Presentations

Drug Utilization

Hina Mehta, PharmD

Drug Use Analyst Office of Surveillance and Epidemiology (OSE) CDER/FDA

Misuse/Abuse of Opioid Analgesics: Findings from The Drug Abuse Warning Network (DAWN)

CatherineDormitzer, PhDOffice of Surveillance and
Epidemiology
CDER/FDA

Medication Errors Postmarketing Safety Review

Of the Manipulation of Oxycodone Immediate-

Products

L. Shenee' Toombs, PharmD

Division of

Medication Error Release

Prevention

OSE/CDER/FDA

ACUROX Efficacy and Safety

Igor Cerny, PharmD
Senior Clinical Analyst
Division of Anesthesia and
Analgesia Products
CDER/FDA

ACUROX Abuse Liability Studies

Jovita Randall-Thompson, PharmD

Pharmacologist Controlled Substance Staff CDER/FDA

Ling Chen, PhD
Mathematical
Statistician, Special
Project Team
CDER/FDA

Open Public Hearing

Questions for the Presenters

Discussion and Questions to the Committee

Adjourn

Ouestions to the Committee

1. Discuss what constitutes an adequate degree of abuse-deterrence to warrant description in the product's label and the potential implications regarding overstating these effects.

There was much discussion by the committee regarding the term "adequate" and where the bar for determining adequacy of a program should be set. That being said, the overall consensus of the committee was that the data presented to the committee would not support a finding that the product adequately addresses the issue of abuse deterrence such that an abuse-deterrence effect would be warranted for inclusion in the product label.

- 2. Based on the results of the studies assessing the effects of niacin on drug liking:
 - (a) Were the studies conducted appropriately to assess the effects of niacin on the abuse liability of oxycodone?

The Committee members did not feel that the sponsor's studies Appropriately addressed the effects of niacin on the abuse liability of oxycodone. There was a concern that the testing did not examine the correct patient population.

(b) If not, what changes should be made to the studies?

The committee members raised concern with the choice of outcome variables used in the studies and several recommended that the sponsor look to those studies conducted to support the pentazocine/naloxone application. The data collected for the outcome variables chosen did not provide compelling evidence to support the concept that the presence of niacin in the Acurox formulation acts as an effective abuse deterrent. Members also suggested that the populations of the patients studied be expanded to include those patients who are actually at risk of becoming abusers of the product, i.e., chronic pain patients at risk and who might be expected to abuse the product, persons for whom the product has not been prescribed, such as family members of taking the product.

(c) Is the presence of niacin in the formulation a potentially effective deterrent?

Overall, the committee did not agree with the sponsor that a rationale basis existed for the niacin component to act as an effective deterrent. Furthermore, members commented that evidence exists that with long-term use, tolerance to the effect of the niacin may develop; it was suggested that the sponsor design and conduct a trial to investigate this issue. The committee also commented that some research and use experience seems to indicate that abusers may actually seek out the effect, the "high", of the niacin.

(d) Are the effects of ingesting the product with food or aspirin/NSAIDS sufficient to reduce the deterrent effect of niacin to a level that is no longer clinically relevant?

The consensus of the members was that the effect of the niacin component (unpleasant flushing sensation) could easily be overcome and suppressed by the concomitant ingestion of food or aspirin/NSAIDS and that this effect was sufficient to make reduce the effect of the niacin to such an extent as to make it no longer clinically relevant as a abuse deterrent.

3. Was the degree of flushing seen in patients treated in the clinical trials acceptable for this product with properties targeted at deterring misuse and abuse?

In response to this question, the committee raised several concerns: with regards to the flushing, it was noted for many patients, there is a psychological component, not just physical, to the the pain that they experience. As such, the product's flushing side effect experienced by actual and legitimate patients could actually tend to worsen the pain that they're experiencing, rather than treating the pain. The committee also raised the fundamental question as to whether the

sponsor had demonstrated that any amount of flushing, whether mild or severe, is a deterrent to the abuse of a product.

4. Please vote on whether Acurox should be approved for the indication of the treatment of moderate to severe pain taking into consideration your conclusion regarding the deterrent effect of the niacin, as well as the potential deterrent effects of the other features specific to the Acurox formulation of oxycodone.

Vote: Yes-1; No-19; Abstain-0

Committee members overwhelmingly voted that the product not <u>be approved</u> for the proposed indication. Further, they commented, that the sponsor's studies did not appropriately address the effects of niacin on the abuse liability of oxycodone. A major concern was expressed that the testing did not examine the correct patient populations. Further, members commented that additional information, such as that pertaining to patients with chronic pain who require high doses of oxycodone, the effects in younger populations (i.e., teens), and the influence of alcohol use in association with the drug intake, should be collected.

The one committee member who voted yes to to this question commented that he believed that there was value in a program which demonstrated any incremental benefit in increased abuse deterrence of a product. The suggestion that there may be benefit to encouraging sponsors to investigate such findings instead of aiming for "perfection" by requiring a standard of absolute abuse-deterrence was made.