

**Food and Drug Administration  
Center for Drug Evaluation and Research**

**Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting  
March 21, 2013**

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

Topic: The committee met to discuss new drug application (NDA) 204442, PROBUPHINE (buprenorphine hydrochloride and ethylene vinyl acetate) subdermal implant, submitted by Titan Pharmaceuticals, Inc., and its safety and efficacy for the proposed indication of maintenance treatment of opioid dependence.

These summary minutes for the March 21, 2013 Meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration were approved on May 17, 2013.

I certify that I attended the March 21, 2013 meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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/s/  
Minh Doan, PharmD  
Acting Designated Federal Officer  
Psychopharmacologic Drugs Advisory  
Committee (PDAC)

\_\_\_\_\_  
/s/  
Edward C. Covington, MD  
Acting Committee Chairperson, PDAC

## Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting March 21, 2013

The following is the final report of the Psychopharmacologic Drugs Advisory Committee meeting held on March 21, 2013. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anesthesia, Analgesia, and Addiction Products and posted on the Food and Drug Administration (FDA) website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm341479.htm>.

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

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The Psychopharmacologic Drugs Advisory Committee of the FDA, Center for Drug Evaluation and Research, met on March 21, 2013, 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 briefing materials from FDA and Titan Pharmaceuticals, Inc. The meeting was called to order by Edward C. Covington, MD (Acting Chairperson), and the conflict of interest statement was read into the record by Minh Doan, PharmD (Acting Designated Federal Officer). There were approximately 150 people in attendance. There were 11 Open Public Hearing speakers.

**Issue:** The committee met to discuss new drug application (NDA) 204442, PROBUPHINE (buprenorphine hydrochloride and ethylene vinyl acetate) subdermal implant, submitted by Titan Pharmaceuticals, Inc., and its safety and efficacy for the proposed indication of maintenance treatment of opioid dependence.

**Attendance:**

**Psychopharmacologic Drugs Advisory Committee Members Present (Voting):**

Victor De Gruttola, ScD; Michael Y. Hwang, MD; Christopher J. Kratochvil, MD; Elizabeth McCarthy, MA, LPC (*Consumer Representative*)

**Psychopharmacologic Drugs Advisory Committee Members Not Present (Voting):**

David A. Brent, MD (*Chairperson*); Murray B. Stein, MD, MPH

**Psychopharmacologic Drugs Advisory Committee Members Not Present (Non- Voting):**

David Michelson, MD (*Industry Representative*)

**Temporary Members (Voting):**

Louis E. Baxter, Sr., MD, FASAM; Vernon M. Chinchilli, PhD; Edward C. Covington, MD (*Acting Chairperson*); Eve Espey, MD, MPH; Adam J. Gordon, MD, MPH; Geri Hewitt, MD; Judith M. Kramer, MD, MS; Laura F. McNicholas, MD, PhD; Robert Steinbrook, MD; Michael L. Yesenko, MDiv (*Patient Representative*); Daniel Zelterman, PhD

**Acting Industry Representative to the Committee (Non-Voting):**

Richard L. Leff, MD (*Acting Industry Representative*)

**FDA Participants (Non-Voting):**

Bob A. Rappaport, MD; Rigoberto Roca, MD; Celia Winchell, MD

**Acting Designated Federal Officer (Non-Voting):**

Minh Doan, PharmD

**Open Public Hearing Speakers:**

Genie L. Bailey, MD; Terry K. Duffel; Jody L. Green, PhD, CCRP (Denver Health & Hospital Authority RADARS® System); Robert Gianbrone; Brent Hunt (Alliance for the Adoption of Innovation in Medicine); Timothy P. Lepak (The National Alliance of Advocates for Buprenorphine Treatment); Walter Ling, MD; Stacy Sigmon, PhD; Matthew A. Torrington, MD; Cynthia Moreno Tuohy (NAADAC-The Association for Addiction Professionals); Elmer Yu, MD, FASAM (statement read by Matthew A. Torrington, MD)

*The agenda proceeded as follows:*

**CALL TO ORDER AND INTRODUCTION  
OF COMMITTEE**

**Edward C. Covington, MD**  
Acting Chairperson, PDAC

**CONFLICT OF INTEREST STATEMENT**

**Minh Doan, PharmD**  
Acting Designated Federal Officer, PDAC

**FDA INTRODUCTORY REMARKS**

**Celia Winchell, MD**  
Clinical Team Leader  
Division of Anesthesia, Analgesia, and Addiction  
Products (DAAAP)  
Office of Drug Evaluation II (ODEII)  
Office of New Drugs (OND), CDER, FDA

**SPONSOR PRESENTATIONS**

**TITAN PHARMACEUTICALS, INC.**

Introduction

**Marc Rubin, MD**  
Executive Chairman  
Titan Pharmaceuticals, Inc.

Background and Medical Need

**Andrea Barthwell, MD, FASAM**  
Former Deputy Director of Demand Reduction Office of  
National Drug Control Policy (ONDCP)  
Founder and CEO of the Two Dreams Treatment System

Clinical Efficacy

**Kate Glassman-Beebe, PhD**  
Executive Vice President and Chief Development Officer  
Titan Pharmaceuticals, Inc.

**SPONSOR PRESENTATIONS (CONT.)**

Clinical Safety

**Steve Chavoustie, MD**  
Segal Institute for Clinical Research

Risk Evaluation and Mitigation Strategy  
(REMS)

**Garry Neil, MD**  
Head of Research & Development  
Braeburn Pharmaceuticals, Inc.

Conclusion

**Kate Glassman-Beebe, PhD**

Clarifying Questions

**BREAK**

**FDA PRESENTATIONS**

Review of Probuphine Clinical Data:  
Efficacy and Safety

**Rachel Skeete, MD**  
Clinical Reviewer  
DAAAP, ODEII, OND, CDER, FDA

**David Petullo, MS**  
Statistics Reviewer  
Division of Biostatistics II, Office of Biostatistics  
Office of Translational Sciences, CDER, FDA

Contraceptive Implants: Regulatory  
History and Lessons Learned

**Barbara Wesley, MD, MPH**  
Clinical Reviewer  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III, OND, CDER, FDA

Clarifying Questions

**LUNCH**

**FDA PRESENTATIONS (CONT.)**

Risk Evaluation and Mitigation Strategy  
for Probuphine

**Jason Bunting, PharmD**  
Risk Management Analyst  
Division of Risk Management, Office of Medication  
Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
CDER, FDA

Clarifying Questions

**OPEN PUBLIC HEARING**

**BREAK**

**CHARGE TO THE COMMITTEE**

**Celia Winchell, MD**

**QUESTIONS TO THE  
COMMITTEE/COMMITTEE DISCUSSION**

**ADJOURNMENT**

***Questions to the Committee:***

1. **DISCUSSION:** Please comment on whether the Applicant conducted adequate dose exploration in the development program to determine the most effective dose.

*Committee Discussion:* The committee members noted that a dose-finding study has not been conducted and there were insufficient data on an appropriate dose range for Probuphine. The committee members also expressed concerns that plasma levels of buprenorphine from 4 – 5 Probuphine subdermal implants were not equivalent to plasma levels attained with the standard 16 milligram dose of sublingual buprenorphine used to treat patients with opioid dependence. In addition, the need for sublingual buprenorphine as rescue therapy in treatment groups provided further justification that additional studies on dosing are necessary. The committee members also had questions on dosing of Probuphine for patients who may require more or less than standard dosing. However, the sponsor noted their intent was to target a population that could be adequately controlled on the standard 12 to 16 milligram dose of sublingual buprenorphine. As such, the committee noted that there has not been adequate dose exploration in the development program to determine the most effective dose. Please see the transcript for details of the committee’s discussion.

- a. **VOTE:** Do the data from the clinical trials provide substantial evidence of effectiveness of Probuphine for the maintenance treatment of opioid dependence?

Yes: 10      No: 5      Abstain: 0

*Committee Discussion:* The majority of the committee agreed that the data from the clinical trials provide substantial evidence of effectiveness of Probuphine for the maintenance treatment of opioid dependence. The committee members who voted “Yes” noted that the data showed that Probuphine was more effective than placebo, as efficacious as other products currently on the market, and the primary endpoint criteria were met. However, they also expressed that further dose exploration was still necessary. The committee members who voted “No” noted that their concern was that optimal dosing has not been determined. Please see the transcript for details of the committee’s discussion.

2. **DISCUSSION:** Please comment on the Applicant’s assessment of the safety aspect of Probuphine in general, as well as on safety concerns specific to the placement and removal of the implants.

*Committee Discussion:* In general, members did not express concerns with the safety of Probuphine. Members commented that the abundance of data on the safe use of implantable contraceptives diminished safety concerns related to the placement and removal of

*Probuphine implants, which uses similar technology. However, members noted there were differences between the population of patients that would use implantable contraceptives and the population of patients that would use Probuphine. Members felt that training for placement and removal of the implants was important to minimize safety concerns. Please see the transcript for details of the committee's discussion.*

- a. **VOTE:** Has the Applicant adequately characterized the safety profile of Probuphine in this patient population?

Yes: 12      No: 2      Abstain: 1

**Committee Discussion:** *The majority of the committee agreed that the Applicant has adequately characterized the safety profile of Probuphine in this patient population. The committee members who voted "Yes" had little concerns regarding safety given the known clinical experience with both sublingual buprenorphine and implantable contraceptives. The committee members who voted "No" and those who voted "Yes" agreed that additional data on the actual use of the product were necessary, particularly with the implantation procedure. One committee member who abstained commented that it is unknown whether the data support safe use. Please see the transcript for details of the committee's discussion.*

3. **VOTE:** Is the Risk Evaluation and Mitigation Strategy (REMS) proposed by the Applicant, which consists of restricted distribution and a training/certification program for healthcare professionals who will implant the product, adequate to address the risks of potential complications associated with the implantation procedure and abuse, misuse, and accidental overdose. Include in your deliberations any concerns related to the proposed model of care and training/certification program.

Yes: 5      No: 4      Abstain: 6

**Committee Discussion:** *There was no consensus among the committee members as to whether the REMS proposed by the Applicant is adequate to address the risks of potential complications associated with the implantation procedure and abuse, misuse, and accidental overdose. The committee members who voted "Yes" noted that the restricted distribution and training/certification program presented by the Applicant was adequate to address the risks of potential complications. It was mentioned that, although there may be a steep learning curve for the implantation procedure, a high volume provider would have no problems with the procedure. However, members did express concerns with the interaction between DATA-2000 waived providers and other healthcare professionals that would implant the product. The committee members who voted "No" expressed concerns with the training/certification program. Concerns were raised regarding whether providers would be trained, not whether they could be trained, to perform the implantation procedure. In addition, these members indicated that potential complications such as abuse and misuse were not fully addressed. Six committee members abstained from voting on this question, noting that the Applicant presented a modified REMS that was not previously described in the briefing materials. Please see the transcript for details of the committee's discussion.*

4. **DISCUSSION:** Please discuss whether the absence of any information on each of the following matters should be considered a critical deficiency in the application:

- a. the potential for removal of the implants by non-medical personnel for the purpose of diversion.

**Committee Discussion:** *The committee members did not express concerns regarding removal of the implants by non-medical personnel for the purpose of diversion. Please see the transcript for details of the committee's discussion.*

- b. the potential for long-term exposure to the components of the rods if an individual never has the implants removed.

**Committee Discussion:** *The committee members did not express concern with long-term exposure of the components of the rods. Please see the transcript for details of the committee's discussion.*

- c. the potential for patients to require implantation into an arm which has received an implant previously in order to remain on treatment, which would necessitate identification of multiple implantation sites per arm, or use of previously implanted sites.

**Committee Discussion:** *The committee members expressed concern with limited implantation sites, but did not feel that it was a critical deficiency. It was noted that sites other than the arms should be explored as long-term treatment could be necessary for some patients. Please see the transcript for details of the committee's discussion.*

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

Yes: 10      No: 4      Abstain: 1

**Committee Discussion:** *The majority of the committee agreed that, based on the data presented and discussed, the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application. The committee members who voted "Yes" noted that, although they voted "Yes," additional data were needed to fully assess both the safety and efficacy of Probuphine and that the REMS was still an area of concern. Overall, these members indicated that the benefits outweighed the risks. The committee members who voted "No" noted that the dose exploration was inadequate and expressed concerns with the REMS. However, these members commented that the product would be approvable once these data become available. The one member who abstained noted similar concerns with the REMS and felt that additional data, particularly regarding patient selection, was needed for a decisive vote. Please see the transcript for details of the committee's discussion.*

*The meeting was adjourned at approximately 5:10 p.m.*