

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

**Summary Minutes of the Anesthetic and Analgesic Drug Products  
Advisory Committee Meeting  
February 14-15, 2018**

Location: FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), 10903 New Hampshire Ave, Silver Spring, Maryland.

Topic: The committee discussed supplemental new drug application (sNDA) 022496/S-009, for EXPAREL (bupivacaine liposomal injectable suspension), submitted by Pacira Pharmaceuticals, Inc., to produce local analgesia and as a nerve block to produce regional analgesia.

These summary minutes for the February 14-15, 2018 meeting of the Anesthetic and Analgesic Drug Products Advisory Committee of the Food and Drug Administration were approved on April 11, 2018.

I certify that I attended the February 14-15, 2018 meeting of the Anesthetic and Analgesic Drug Products Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

\_\_\_\_\_/s/\_\_\_\_\_  
Moon Hee V. Choi, PharmD  
Designated Federal Officer, AADPAC

\_\_\_\_\_/s/\_\_\_\_\_  
Mary Ellen McCann, MD, MPH  
Acting Chairperson, AADPAC

**Summary Minutes of the Anesthetic and Analgesic Drug Products  
Advisory Committee Meeting  
February 14-15, 2018**

The following is the final report of the Anesthetic and Analgesic Drug Products Advisory Committee meeting held on February 14-15, 2018. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anesthesia, Analgesia, and Addiction Products and posted on the FDA website at:

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm591101.htm>.

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

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The Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on February 14-15, 2018, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Pacira Pharmaceuticals, Inc. The meeting was called to order by Mary Ellen McCann, MD, MPH, (Acting Chairperson). The conflict of interest statement was read into the record by Moon Hee Choi, PharmD (Designated Federal Officer). There were approximately 100 people in attendance. There were 15 Open Public Hearing (OPH) speaker presentations.

**Issue:** The committee discussed supplemental new drug application (sNDA) 022496/S-009, for EXPAREL (bupivacaine liposomal injectable suspension), submitted by Pacira Pharmaceuticals, Inc., to produce local analgesia and as a nerve block to produce regional analgesia.

**Attendance:**

**Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting):** David S. Craig, PharmD; Jeffrey L. Galinkin, MD, FAAP; Jennifer G. Higgins, PhD (Consumer Representative); Ronald S. Litman, DO; Mary Ellen McCann, MD, MPH (Acting Chairperson); Abigail B. Shoben, PhD; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP

**Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting):** Brian T. Bateman, MD, MSc; Raeford E. Brown, Jr., MD, FAAP, Lonnie Zeltzer, MD

**Anesthetic and Analgesic Drug Products Advisory Committee Member Not Present (Non-Voting):** W. Joseph Herring, MD, PhD (Industry Representative)

**Temporary Members (Voting):** Padma Gulur, MD; Laura D. Porter, MD (Patient Representative); Gregory Terman, MD, PhD

**Acting Industry Representative to the Anesthetic and Analgesic Drug Products Advisory Committee (Non-Voting):** Michele Hummel, PhD, RPh (Acting Industry Representative)

**FDA Participants (Non-Voting):** Sharon Hertz, MD; Rigoberto Roca, MD; Alla Bazini, MD; David Petullo, MS; Yun Xu, PhD

**Designated Federal Officer (Non-Voting):** Moon Hee V. Choi, PharmD

**Open Public Hearing Speakers:** Drew Havard, DMD (on behalf of Pedro F. Franco, DDS); Xiaodong Bao, MD, PhD; Jim Moser, CST; Mary Bono; Christopher F. Tirotta, MD, MBA; Daniel I. Sessler, MD; Andy Moore, MD (Surgery on Sunday); Gary Mendell (Shatterproof); Stacy Litz (Choices Matters); Danielle Shapiro, MD, MPH (National Center for Health Research); Robert C. Steele; Michael A. Mont, MD; Beverly A. Woods; Michael Kent, MD; Patrick Ivan Borgen, MD

*The agenda was as follows:*

**Day 1: February 14, 2018**

Call to Order and Introduction of Committee

**Mary Ellen McCann, MD, MPH**  
Acting Chairperson, AADPAC

Conflict of Interest Statement

**Moon Hee V. Choi, PharmD**  
Designated Federal Officer, AADPAC

FDA Introductory Remarks

**Sharon Hertz, MD**  
Director  
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)  
Office of Drug Evaluation II (ODE-II)  
Office of New Drugs (OND), CDER, FDA

**APPLICANT PRESENTATIONS**

**Pacira Pharmaceuticals, Inc.**

Introduction

**Michael Rozycki, PhD**  
Vice President, Regulatory Affairs  
Pacira Pharmaceuticals, Inc.

Unmet Need

**Anoushka Afonso, MD**  
Director, Enhanced Recovery after Surgery  
Department of Anesthesiology & Critical Care  
Memorial Sloan Kettering Cancer Center

Efficacy

**Roy S. Winston, MD**  
Sr Vice President  
Anesthesia, Surgery, and Medical Affairs  
Pacira Pharmaceuticals, Inc.

**APPLICANT PRESENTATIONS (CONT.)**

Safety

**Richard Scranton, MD, MPH**  
Sr Vice President and Chief Scientific Officer  
Pacira Pharmaceuticals, Inc.

Clinical Perspective

**Jeff Gadsden, MD, FRCPC, FANZCA**  
Associate Professor  
Duke University School of Medicine  
Chief, Division of Orthopaedic, Plastic and  
Regional Anesthesiology  
Regional Anesthesiology and Acute Pain  
Medicine Fellowship Director  
Duke University Medical Center

Conclusions

**Richard Scranton, MD, MPH**

**BREAK**

Clarifying Questions

**ADJOURNMENT**

**Day 2: February 15, 2018**

Call to Order

**Mary Ellen McCann, MD, MPH**  
Acting Chairperson, AADPAC

Conflict of Interest Statement

**Moon Hee V. Choi, PharmD**  
Designated Federal Officer, AADPAC

FDA Introductory Remarks

**Sharon Hertz, MD**  
Director  
DAAAP, ODE-II, OND, CDER, FDA

**FDA PRESENTATIONS**

Assessment of Efficacy Data of Studies  
Submitted in Support of sNDA

**Alla Bazini, MD**  
Medical Officer  
DAAAP, ODE-II, OND, CDER, FDA

Statistical Review of EXPAREL Efficacy  
from Nerve-block Studies

**Katherine Meaker, MS**  
Statistics Reviewer  
Division of Biometrics II  
Office of Biostatistics  
Office of Translational Sciences (OTS)  
CDER, FDA

**FDA PRESENTATIONS (CONT.)**

Pharmacokinetics (PK) of EXPAREL from Infiltration and Nerve-block Studies      **Suresh Naraharisetti, DVM, PhD**  
Clinical Pharmacology Reviewer  
Division of Clinical Pharmacology II  
Office of Clinical Pharmacology (OCP)  
OTS, CDER, FDA

Assessment of Safety Data of Studies Submitted in Support of sNDA      **Alla Bazini, MD**

**BREAK**

Clarifying Questions

**LUNCH**

Open Public Hearing

Charge to the Committee      **Sharon Hertz, MD**

Questions to the Committee/Committee Discussion

**BREAK**

Questions to the Committee/Committee Discussion

**ADJOURNMENT**

***Questions to the Committee:***

1. **DISCUSSION:** What efficacy data are necessary to adequately evaluate the benefit of Exparel for nerve block?
  - a. Discuss whether active comparator arms should be included in future efficacy studies of Exparel
  - b. Discuss any circumstances where placebo-controlled studies alone are adequate to evaluate the efficacy of Exparel

***Committee Discussion:*** *The majority of the committee expressed that an active comparator arm should be included in future efficacy studies of Exparel. One committee member mentioned that active comparator arms would be necessary if the applicant wanted to make any superiority claims of Exparel over bupivacaine. One committee member agreed that placebo-controlled studies alone are adequate to evaluate the efficacy of Exparel as long as efficacy is demonstrated; however, another committee member disagreed by stating that placebo-controlled studies alone would not be adequate to determine efficacy when treating*

*post-surgical pain. Another committee member noted that in order to evaluate the efficacy of Exparel in terms of outcomes, adequate long-term data is needed to support an “opioid-sparing” claim. Please see the transcript for details of the committee discussion.*

**2. DISCUSSION:** The applicant has requested that Exparel be indicated “as a nerve block to produce regional analgesia.”

- a. Discuss whether the efficacy data support the use of Exparel as a nerve block for the femoral nerve, intercostal nerves, or brachial plexus
- b. Discuss whether the data support any of the following:
  - i. a broad indication for nerve block
  - ii. individual nerve block indications
  - iii. no nerve block indication
- c. If you do not find the data adequate to support any nerve block indication, describe the data that would be necessary to support this indication.

***Committee Discussion:** Overall, the majority of the committee agreed that efficacy was demonstrated to support the use of Exparel as a nerve block for the brachial plexus. Most committee members agreed that the efficacy data to support the use of Exparel as a nerve block for the femoral nerve is contradictory. All of the committee agreed that efficacy was not demonstrated to support the use of Exparel as a nerve block for the intercostal nerves. Some committee members noted that a larger sample size would be needed to help better assess the efficacy of Exparel. Other committee members added that because of the variability in patients, reproducible data would further help support the use of Exparel for the brachial plexus. The majority of the committee agreed that the data does not support a general nerve block indication. One committee member expressed concern for the use of Exparel for individual nerve block indications as historically, local anesthetics have not been approved for use in individual nerve blocks, and stated that practitioners would face a difficult challenge when having to narrow its use. However, one committee member disagreed, stating that the data support the use of Exparel as a nerve block for the femoral and interscalene nerves and would support a general nerve block indication. Some committee members agreed that the grouping of the studies in the femoral nerve, intercostal nerves and the brachial plexus was a positive demonstration of the use of Exparel in the lower extremity, truncal area and upper extremities, but found the data conflicting and confounding with many short-comings. These committee members agreed that an active comparator arm and a larger sample size would help support the proposed indication. Please see the transcript for details of the committee discussion.*

**3. DISCUSSION:** What safety data are necessary to adequately evaluate the risks of Exparel for nerve block?

- a. Discuss whether active comparator arms should be included in future studies of Exparel

- b. Discuss whether there are circumstances where placebo-controlled studies or open-label studies are adequate to assess the safety of Exparel
- c. Discuss whether the safety data submitted are adequate to characterize the safety profile of Exparel

**Committee Discussion:** *One committee member stated that further studies need to be done, and that active comparators in future studies should be those that are standard of care in one's own practice or an institution's practice of equipoise. Some committee members agreed that the safety data submitted was not adequate to characterize the safety profile of Exparel and expressed concerns associated with the increased deaths and safety associated with the falls. One committee member suggested a non-clinical study with an active comparator and Exparel to determine what dose would lead to toxicity and demonstrate that an overdose can be successfully treated with an intralipid. Another committee member noted that it would be difficult to execute a study on safety without a large sample size, and suggested a registry for nerve blocks to compare incidences of using regular local anesthetics to long-acting anesthetics to include other complications experienced. Most committee members agreed that "opioid sparing" is not a valuable safety endpoint. One committee member added that data is needed to compare dose in relation to either pain intensity or functional outcome to determine the relationship between the two to provide context. Some committee members noted that the current existing label for Exparel states that "bupivacaine should not be administered within 96 hours following Exparel," but this information is incomplete so the label should instead state that no local anesthetics should be administered within 96 hours following administration of Exparel. Please see the transcript for details of the committee discussion.*

- 4. DISCUSSION:** Please discuss whether the data are adequate to support a change in the proposed indication from "administration into the surgical site to produce postsurgical analgesia" to "single-dose infiltration to produce local analgesia".

**Committee Discussion:** *The majority of the committee agreed that the data is not adequate to support a change in the proposed indication from "administration into the surgical site to produce post-surgical analgesia" to "single-dose infiltration to produce local analgesia". One committee member noted that one of the indications was already "single dose infiltration to produce local analgesia" but not labeled as such. Other committee members suggested combining the proposed indications to "single-dose infiltration to produce post-surgical analgesia". Please see the transcript for details of the committee discussion.*

- 5. DISCUSSION:** Please discuss any outstanding issues with this supplemental NDA that warrant additional studies, and if so, should these studies be conducted before or after approval.

**Committee Discussion:** *The majority of the committee members agreed that additional studies are needed. There was no overall consensus that these studies needed to be conducted before or after approval. One committee member noted that longevity data is needed to*

*support the “opioid-sparing” claim. Please see the transcript for details of the committee discussion.*

**6. VOTE:** Do the data submitted support approval of an additional indication for nerve block?

**Vote Result:**      Yes: 4            No: 6            Abstain: 0

***Committee Discussion:*** *The majority of the committee agreed that the data submitted did not support approval of an additional indication for nerve block. Some of the committee members who voted “No” agreed that some efficacy was demonstrated but had major concerns with safety. Some members who voted “Yes” also indicated that they would like to see additional studies; however, they did not specify whether these should be conducted pre- or post-marketing. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 2:56 p.m.