

**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.

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.