

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

**Summary Minutes of the
Endocrinologic and Metabolic Drugs Advisory Committee Meeting
September 12, 2014**

Location: The Marriott Inn and Conference Center, University of Maryland University College (UMUC), Potomac Ballroom, 3501 University Blvd. East, Hyattsville, Maryland.

Topic: The committee discussed biologics license application (BLA) 125511, proposed trade name NATPARA (established name: Recombinant Human Parathyroid Hormone (rDNA) or (rhPTH[1-84])), submitted by NPS Pharmaceuticals, Inc., for the proposed indication of replacement for endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism

These summary minutes for the September 12, 2014, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on October 10, 2014.

I certify that I attended the September 12, 2014, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

-signed-
Karen Abraham-Burrell, PharmD
Designated Federal Officer, EMDAC

-signed-
Robert J. Smith, MD
Chairperson, EMDAC

**Summary Minutes of the Endocrinologic and Metabolic Drugs
Advisory Committee Meeting
September 12, 2014**

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting held on September 12, 2014. A verbatim transcript will be available in approximately six weeks, sent to the Division of Metabolism and Endocrinology Products and posted on the FDA website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm386727.htm>

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

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on September 12, 2014 at the Marriott Inn and Conference Center, University of Maryland University College (UMUC), Potomac Ballroom, 3501 University Blvd. East, Hyattsville, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA and NPS Pharmaceuticals. The meeting was called to order by Robert J. Smith, MD (Chairperson); the conflict of interest statement was read into the record by Karen Abraham-Burrell, PharmD (Designated Federal Officer). There were approximately 75 people in attendance. There were 14 Open Public Hearing speakers.

Issue: The committee discussed biologics license application (BLA) 125511, proposed trade name NATPARA (established name: Recombinant Human Parathyroid Hormone (rDNA) or (rhPTH[1-84]), submitted by NPS Pharmaceuticals, Inc., for the proposed indication of replacement for endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism.

Attendance:

EMDAC Members Present (Voting): Diana Hallare, MPH (Consumer Representative); Robert J. Smith, MD (Chairperson); Charles A. Stanley, MD

EMDAC Members Present (Non-Voting): Mads F. Rasmussen, MD, PhD (Industry Representative)

EMDAC Members Not Present (Voting): David W. Cooke, MD; William R. Hiatt MD, FACP; Peter W.F. Wilson MD; Ed J. Hendricks, MD

Temporary Members (Voting): Carola Arndt, MD; Diane M. Biskobing, MD; Susan Rice Broyles (Patient Representative). Daniel Gillen, PhD; Susan R. Heckbert, MD, PhD; Julia Lewis, MD; Kevin McBryde, MD, Martha Nason, PhD; Thomas J. Weber, MD; Lee S. Weinstein, MD

September 12, 2014

Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee

FDA Participants (Non-Voting): Curtis J. Rosebraugh, MD; Jean-Marc Guettier, MD, CM; Dragos Roman, MD; Manoj Khurana, PhD; Naomi Lowy, MD

Designated Federal Officer (Non-Voting): Karen Abraham-Burrell, PharmD

Open Public Hearing Speakers: James Sanders (Hypoparathyroidism Association, Inc.); George Grunberger (American Association of Clinical Endocrinologists (AACE)); Becky Buckman on behalf of Michele West; Becky Buckman; Gail Rosenberg; Carol Sanders; Keith Smet; Jill Hartmann; Meghan Hartman; Diane Dorman (National Organization for Rare Disorders (NORD)); Jen Melanson; Danielle Anderson; CeCe Donoghue; Gary Bloom (Thyroid Cancer Survivor's Association, Inc.)

The agenda proceeded as follows:

Call to Order and Introduction of Committee

Robert J. Smith, MD
Chairperson, EMDAC

Conflict of Interest Statement

Karen Abraham-Burrell, PharmD
Designated Federal Officer, EMDAC

FDA Introductory Remarks

Jean-Marc Guettier, MD
Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II (ODE II)
Office of New Drugs (OND), CDER, FDA

APPLICANT PRESENTATIONS

NPS Pharmaceuticals, Inc.

Introduction

Robert Ashworth, PhD
Vice President, Global Regulatory Affairs
NPS Pharmaceuticals

Unmet Need

Tamara Vokes, MD
Professor of Medicine
Director, Osteoporosis & Metabolic Bone Disease
The University of Chicago Medical Center

Efficacy

Hjalmar Lagast, MD
Vice President, Clinical Development
NPS Pharmaceuticals

APPLICANT PRESENTATIONS (cont.)

Safety **Ralf Roskamp, MD**
Vice President, Global Clinical Development
NPS Pharmaceuticals

Conclusion **Roger Garceau, MD**
Chief Medical Officer
NPS Pharmaceuticals

Clarifying Questions

BREAK

FDA PRESENTATIONS

Natpara Clinical Efficacy and Safety
Review **Naomi Lowy, MD**
Medical Officer
DMEP, ODE II, OND, CDER, FDA

FDA Review of the Nonclinical
Carcinogenicity Assessment **Ronald Wange, PhD**
Supervisory Pharmacologist
DMEP, ODE II, OND, CDER, FDA

Clinical Pharmacology Review of
Natpara **Manoj Khurana, PhD**
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology II (DCP II)
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS)
CDER, FDA

Clarifying Questions

LUNCH

Open Public Hearing

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss whether the data in the REPLACE trial provide substantial evidence that treatment with Natpara offers a clinically meaningful benefit to patients with hypoparathyroidism regardless of etiology. In your discussion, specifically address this (or these) benefit(s).

Committee Discussion: *The majority of the committee agreed that the data in the REPLACE trial provided substantial evidence that treatment with Natpara offers benefit to patients with hypoparathyroidism, in terms of decreasing daily calcium and vitamin D requirement, but there is uncertainty regarding how this addresses the actual clinical need in patients. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Discuss your level of concern with regard to the risks (acute and chronic) of hypercalcemia and hypocalcemia associated with the use of Natpara. Comment on ways to mitigate these risks in the clinical care setting.

Committee Discussion: *The majority of the committee agreed that there is a low level of concern with regard to the risk of hypercalcemia associated with the use of Natpara. The committee did express the need for frequent monitoring of calcium levels while being treated with Natpara. Conversely, the majority of the committee agreed that there is a higher level of concern with regard to the risk of hypocalcemia associated with the use of Natpara. The committee agreed that providing guidance to physicians on the risk of hypocalcemia and frequent monitoring would be appropriate for mitigating the risk. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Discuss your level of concern with regard to the risk of osteosarcoma associated with long-term use of Natpara in patients with hypoparathyroidism. In your discussion, specifically address how differences or similarities between a population of patients with osteoporosis and a population of patients with hypoparathyroidism does or does not inform your assessment of this risk.

Committee Discussion: *The majority of the committee agreed that the level of concern with regard to osteosarcoma associated with long-term use of Natpara in patients with hyperparathyroidism is significant. The committee acknowledged that the data are inadequate to resolve their questions, but given the serious nature of osteosarcoma, the committee agreed that there should be some effort to mitigate the risk. Please see the transcript for details of the committee discussion.*

4. **DISCUSSION:** Discuss any additional concerns you may have related to risks or benefit not raised above.

Committee Discussion: *The committee commented on the following additional concerns related to risk or benefit of Natpara:*

- *Identify a subgroup of patients that might benefit from different administration or different dosing than proposed by the sponsor*
- *Address quantitatively the quality of life benefit for patients being treated with Natpara*

Please see the transcript for details of the committee discussion.

5. **VOTE:** In light of the efficacy and safety findings in the Natpara development program, does the overall risk-benefit of Natpara administered at the doses and regimen proposed support approval of Natpara for the long-term treatment of hypoparathyroidism?
- a. If voting YES, please provide your rationale and whether you recommend any additional studies post-approval.
 - b. If voting NO, please provide your rationale and discuss what additional data would be necessary prior to approval to address your concerns.

Vote Result: **Yes – 8** **No – 5** **Abstain – 0**

Committee Discussion: *A slight majority of the committee agreed that the overall risk-benefit of Natpara administered at the doses and regimen proposed support approval of Natpara for the long-term treatment of hypoparathyroidism. The committee members who voted “Yes” made the following recommendations for additional studies post-approval:*

- *Follow-up safety studies on osteosarcoma*
- *Studies of a more frequent dosing interval*
- *Require mandatory reporting of osteosarcoma*
- *Education of prescribers and patients*

The committee members who voted “No” indicated that the following would be necessary prior to approval to address concerns:

- *Studies of a more frequent dosing and a titration schedule*
- *Studies powered to show objective quality of life data that show a quality of life benefit*
- *Studies on the effects on serum calcium levels*
- *Studies for osteosarcoma*
- *Studies on subgroups of patients that are likely to benefit*

Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 4:51 p.m.