

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125511Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**  
**Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: January 23, 2015

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer  
Division of Risk Management (DRISK)  
Kate Oswell, MA, Health Communications Analyst, DRISK

DRISK Team Leader: Naomi Redd, Pharm D, Acting Team Leader, DRISK

Division Director: Cynthia LaCivita, Pharm.D, Acting Director DRISK

Subject: Evaluation of second and third set of REMS documents submitted via email on January 23, 2015

Drug Name(s): Natpara<sup>®</sup>, recombinant Human Parathyroid Hormone [rhPTH (1-84)] for injection

Therapeutic Class: Parathyroid hormone

Dosage and Route: 25 mcg, 50 mcg, 75 mcg, and 100 mcg; subcutaneous injection

Application Type/Number: BLA 125511

Submission Number: email submission from January 23, 2015

Applicant/sponsor: NPS Pharmaceuticals

OSE RCM #: 2013-2500 and 2013-2496

**\*\*\* This document contains proprietary and confidential information \*\*\***  
**that should not be released to the public.**

## 1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of NPS Pharmaceuticals' proposed risk evaluation and mitigation strategy (REMS) documents received by FDA on January 23, 2015 (via email at 4:05 pm and at 5:26 pm). These amendments included all REMS documents.

The following comments were sent to the sponsor regarding the 4:05 pm submission.

<b>Natpara REMS: Summary of Changes</b>
<b>FDA revisions/comments</b> <b>01/23/2015</b> <i>(4:05 pm submission via email)</i>
<b>APPENDIX 1 - NATPARA REMS Document</b>
Replace (b) (4) with (855) 628-7272
<b>APPENDIX 8 - NATPARA REMS Patient-Prescriber Acknowledgment Form</b>
Revise third bullet under Patient Acknowledgement Form to: I understand that I should tell my doctor <b>right away</b> if I have any of the following signs or symptoms that could be associated with osteosarcoma: — pain in any areas of <b>my</b> (b) (4) body that does not go away — any new or unusual lumps or swelling under <b>my</b> (b) (4) skin that is tender to touch”
<b>APPENDIX 12 - NATPARA REMS Supporting Document</b>
Page 24, REMS Message Map for patients - Please delete the following: (b) (4)  (b) (4)

NPS submitted a REMS amendment for Natpara at 5:26 pm on January 23, 2015 to address the list of comments above.

## 2 MATERIALS REVIEWED

### 2.1 INFORMATION SOURCES

- Amariyls Vega, MD, MPH/ Kate Oswell, MA, REMS Review for Natpara, dated June 19, 2014.
- Amariyls Vega, MD, MPH/ Kate Oswell, MA, REMS Review for Natpara, dated December 12, 2014.
- Amariyls Vega, MD, MPH/ Kate Oswell, MA, REMS Review for Natpara, dated December 23, 2014.
- Amariyls Vega, MD, MPH/ Kate Oswell, MA, REMS Review for Natpara, dated January 16, 2015.

- Amariyls Vega, MD, MPH/ Kate Oswell, MA, REMS Review for Natpara, dated January 22, 2015.
- Amariyls Vega, MD, MPH/ Kate Oswell, MA, REMS Review for Natpara, dated January 23, 2015.
- Kendra Jones, OPDP REMS Consult Review, signed in DARRTS on January 16, 2015
- NPS proposed REMS for Natpara amended submissions (email), dated January 23, 2015 at 4:05 pm and 5:26 pm.

### **3 REVIEW RESULTS**

The Applicant included all the revisions requested by DRISK on January 23, 2015.

### **4 CONCLUSIONS AND RECOMMENDATIONS**

The amendments to the Natpara REMS submitted by NPS on January 23, 2015 at 4:05 pm and 5:26 pm included all the revisions requested by DRISK. DRISK recommends approval of the Natpara REMS. The REMS document and all REMS materials are appended to this review.

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/s/  
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AMARILYS VEGA  
01/23/2015

CYNTHIA L LACIVITA  
01/23/2015  
Concur

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

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Division of Risk Management (DRISK)  
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Subject: Evaluation of REMS Documents submitted via email on January 23, 2015

Drug Name(s): Natpara<sup>®</sup>, recombinant Human Parathyroid Hormone [rhPTH (1-84)] for injection

Therapeutic Class: Parathyroid hormone

Dosage and Route: 25 mcg, 50 mcg, 75 mcg, and 100 mcg; subcutaneous injection

Application Type/Number: BLA 125511

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## **1 INTRODUCTION**

This review documents the Division of Risk Management's (DRISK) evaluation of NPS Pharmaceuticals' proposed risk evaluation and mitigation strategy (REMS) documents received by FDA on January 23, 2015 (via email). This amendment includes all REMS documents.

## **2 MATERIALS REVIEWED**

### **2.1 INFORMATION SOURCES**

- Amarilys Vega, MD, MPH/ Kate Oswell, MA, REMS Review for Natpara, dated June 19, 2014.
- Amarilys Vega, MD, MPH/ Kate Oswell, MA, REMS Review for Natpara, dated December 12, 2014.
- Amarilys Vega, MD, MPH/ Kate Oswell, MA, REMS Review for Natpara, dated December 23, 2014.
- Amarilys Vega, MD, MPH/ Kate Oswell, MA, REMS Review for Natpara, dated January 16, 2014.
- Amarilys Vega, MD, MPH/ Kate Oswell, MA, REMS Review for Natpara, dated January 22, 2014.
- Kendra Jones, OPDP REMS Consult Review, signed in DARRTS on January 16, 2015
- NPS proposed REMS for Natpara amended submission (email), dated January 23, 2015.

## **3 REVIEW RESULTS**

The Applicant included most of the revisions provided by DRISK in the January 22, 2015 review. Additional comments to the REMS materials are included in section 5 of this review.

After further internal discussion, the Office of Medication Error Prevention and Risk Management (OMEPRM), of which DRISK is a part of, agreed to align with recommendations from the Office of Prescription Drug Promotion (OPDP) to remove the following or similar statements from all REMS documents: (b) (4)

[REDACTED] This statement is not part of the approved indication and is considered by the Agency as promotional in nature. Please refer to OPDP's review by Kendra Jones dated January 16, 2015 and to DRISK review dated January 22, 2015 (entered in DARRTS on January 23, 2015) which includes DRISK's responses to OPDP's comments from January 16, 2015.

## **4 CONCLUSIONS AND RECOMMENDATIONS**

The Natpara REMS proposal submitted by NPS on January 23, 2015 requires a few additional revisions which are listed in section 5 below.

The Natpara REMS can be approved contingent upon the revisions listed in section 5 of this review.

**5 COMMENTS FOR THE APPLICANT**

1. FDA acknowledges receiving on January 23, 2015 your amendment of the Natpara REMS.
2. The following table lists all FDA comments and recommendations.

<b>Natpara REMS: Summary of Changes</b>
<b>FDA revisions/comments 01/23/2015</b>
<b>General Comments</b>
Delete line number in all REMS documents.
After further internal discussion, FDA is requesting NPS to remove the following and similar statements from all REMS documents: [REDACTED] (b) (4) [REDACTED] This statement is not part of the approved indication and is considered by the Agency as promotional in nature.
<b>APPENDIX 1 - NATPARA REMS Document</b>
<b>Line 137:</b> For REMS Document, replace – [REDACTED] (b) (4) with (844-628-7367). In REMS communication materials, include the number (628-7367) after all mentions of 844-NAT-REMS: 844-NAT-REMS (628-7367)
<b>APPENDIX 8 - NATPARA REMS Patient-Prescriber Acknowledgment Form</b>
Revise third bullet under Patient Acknowledgement Form to: I understand that I should tell my doctor if I have any of the following signs or symptoms that could be associated with osteosarcoma:...”
<b>APPENDIX 12 - NATPARA REMS Supporting Document</b>
Update document version number to reflect current date (footer)

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/s/  
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AMARILYS VEGA  
01/23/2015

CYNTHIA L LACIVITA  
01/23/2015  
Concur

## **Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF DRUG EVALUATION II  
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS**

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**NDA/BLA #s:** BLA 125511  
**Products:** NATPARA (parathyroid hormone) for injection  
**APPLICANT:** NPS Pharmaceuticals  
**FROM:** Jennifer Rodriguez Pippins, M.D., M.P.H  
**DATE:** January 12, 2015

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Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

NATPARA (parathyroid hormone) for injection is proposed for use as an adjunct to calcium and active forms of vitamin D to control hypocalcemia in patients with hypoparathyroidism. During the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting held for this application on September 12, 2014, concerns were raised regarding the modest efficacy demonstrated for NATPARA (parathyroid hormone) for injection, particularly in light of the potential risk of osteosarcoma identified from nonclinical data. Following the advisory committee meeting, the requirement for a REMS to provide for a positive benefit: risk balance was discussed internally, including at a REMS Oversight Committee (ROC) meeting held on October 8, 2014, at which the Division of Metabolism and Endocrinology Products (DMEP) and the Division of Risk Management (DRISK) presented their joint recommendation of a REMS with Elements to Assure Safe Use (ETASU). The minimum necessary elements to ensure the benefits of NATPARA outweigh the risks include: prescriber certification, pharmacy certification, documentation of a safe use condition (i.e., Patient-Prescriber Acknowledgment Form informing patients of the potential risk of osteosarcoma). These elements are necessary to mitigate the potential risk of osteosarcoma associated with the use of NATPARA (parathyroid hormone) for injection, particularly in light of the difficulties inherent in communicating a drug risk that is based on nonclinical data, the lack of familiarity with osteosarcoma (a rare cancer) among the likely prescribers, the challenges of weighing benefit: risk in the pediatric population, and the possible inappropriate attribution of benefit given the product's classification as a

hormone (in contrast to currently used therapies, e.g., oral calcium plus vitamin D). With regard to this last point, while Natpara is parathyroid hormone, pharmacokinetic data demonstrate that it does not provide physiologic PTH replacement. Typically endocrine diseases are treated with hormone replacement (e.g., hypothyroidism), which is considered to represent the optimal way to manage a hormone deficiency. The classification of the product, while accurate, may be misconstrued by prescribers and patients as implying benefits that were not substantiated with scientific evidence simply on the basis that the active ingredient in the drug product is identical to the hormone known to be insufficient in this condition. The safe use condition (i.e., Patient-Prescriber Acknowledgment Form) was viewed as necessary by DMEP and DRISK, given that the cornerstone of risk mitigation for this product is appropriate patient selection, and informed and collaborative decision making between the patient and provider is key to supporting such patient selection.

Therefore, after consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for NATPARA (parathyroid hormone) for injection to ensure that the benefits of the drug outweigh the potential risk of osteosarcoma identified from nonclinical studies with NATPARA (parathyroid hormone) for injection. NATPARA can be approved only if such elements are required as part of a strategy to mitigate the potential risk of osteosarcoma, which is listed in the labeling of the drug. In reaching this determination, we considered the following:

- A. Hypoparathyroidism is a rare disease, with an estimated United States patient population of approximately 60,000.<sup>1</sup> The current standard of care for hypoparathyroidism consists of oral supplementation with calcium and vitamin D. It is anticipated that a small percentage of the overall hypoparathyroid patient population will be candidates for NATPARA (parathyroid hormone) for injection, which is intended for patients whose signs and symptoms of hypoparathyroidism are not well-controlled on calcium and vitamin D alone.
- B. Hypoparathyroidism is characterized by parathyroid hormone levels insufficient to maintain normal serum calcium levels. It occurs most commonly as a result of accidental or intentional removal of the parathyroid glands and more rarely in the setting of autoimmune or congenital diseases. The most common symptoms associated with hypoparathyroidism are due to acute hypocalcemia and include numbness, paresthesia, musculoskeletal irritability, seizures, cardiac arrhythmias, and laryngeal spasms; these symptoms are generally reversible with correction of calcium levels. Reported chronic complications of hypoparathyroidism include those pertaining to chronic hypocalcemia (i.e., cardiomyopathy), chronic hypercalciuria (i.e., nephrocalcinosis, nephrolithiasis, and renal impairment), chronic hyperphosphatemia (i.e., central nervous system and vascular extracellular calcification), and to low bow turnover (i.e., increased bone mass and bone fragility).
- C. In a randomized, placebo-controlled trial in patients receiving calcium and vitamin D supplementation, NATPARA (parathyroid hormone) for injection showed a statistically significant difference in a primary composite endpoint (at least a 50% reduction from baseline active vitamin D dose, at least a 50% reduction from the baseline oral calcium dose,

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<sup>1</sup> Powers J et al. Prevalence and incidence of hypoparathyroidism in the United States using a large claims database. *Journal Bone Mineral Research*. December 2013; 28(12):2570-6.

and an albumin-corrected total serum calcium concentration between 7.5 mg/dL and 10.6 mg/dL) compared to placebo.

- D. The expected duration of therapy is over a patient's lifetime.
- E. In addition to the most serious risk of osteosarcoma, NATPARA (parathyroid hormone, human) also carries the risk of both hyper- and hypocalcemia. Osteosarcoma has been identified as a potential risk for NATPARA (parathyroid hormone, human) based on nonclinical data. Osteosarcoma is a rare malignancy of bone, with a background incidence of 1.7 to 4.4 per million, depending on age.<sup>2</sup> With respect to hypercalcemia, during the titration period of the pivotal trial 30% of patients in the NATPARA (parathyroid hormone, human) treatment arm had an elevated albumin-corrected serum calcium level of >10.6 to ≤12 mg/dL compared to 0% of patients in the placebo arm, and 2% had an elevated albumin-corrected serum calcium level of >12 to ≤13 mg/dL compared to 0% of patients in the placebo arm. During the maintenance period of the pivotal trial 10% of patients in the NATPARA (parathyroid hormone, human) treatment arm had an elevated albumin-corrected serum calcium level of >10.6 to ≤12 mg/dL compared to 0% of patients in the placebo arm, and 3% had an elevated albumin-corrected serum calcium level of >12 to ≤13 mg/dL compared to 0% of patients in the placebo arm. With respect to hypocalcemia, an imbalance favoring placebo was observed in the maintenance period of the pivotal trial, with 12 % of patients in the NATPARA (parathyroid hormone, human) treatment arm experiencing an albumin-corrected serum calcium of <7 mg/dL compared to 0% in the placebo arm. The risk of hypocalcemia increases when NATPARA (parathyroid hormone, human) is withdrawn; during the withdrawal phase of the pivotal trial, 17% of patients previously randomized to NATPARA (parathyroid hormone, human) experienced an albumin-corrected serum calcium of <7 mg/dL compared to 5% of patients previously treated with placebo.
- F. NATPARA (parathyroid hormone, human) is a new molecular entity.

The elements of the REMS will be: elements to ensure safe use, including prescriber certification, pharmacy certification, documentation of a safe use condition (i.e., Patient-Prescriber Acknowledgment Form), an implementation system, and a timetable for submission of assessments of the REMS.

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<sup>2</sup> Mirabello L, et al. Osteosarcoma incidence and survival rates from 1973 to 2004: Data from the Surveillance, Epidemiology and End Results Program. *Cancer*. 2009;115, 1531-1543.

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/s/  
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JENNIFER R PIPPINS  
01/23/2015

**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**  
**Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: January 22, 2015

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer  
Division of Risk Management (DRISK)  
Kate Oswell, MA, Health Communications Analyst, DRISK

DRISK Team Leader: Naomi Redd, Pharm D, Acting Team Leader, DRISK

Division Director: Cynthia LaCivita, Pharm.D, Acting Director DRISK

Subject: Evaluation of REMS Documents submitted via email on January 21, 2015

Drug Name(s): Natpara<sup>®</sup>, recombinant Human Parathyroid Hormone [rhPTH (1-84)] for injection

Therapeutic Class: Parathyroid hormone

Dosage and Route: 25 mcg, 50 mcg, 75 mcg, and 100 mcg; subcutaneous injection

Application Type/Number: BLA 125511

Submission Number: email submission from January 21, 2015

Applicant/sponsor: NPS Pharmaceuticals

OSE RCM #: 2013-2500 and 2013-2496

**\*\*\* This document contains proprietary and confidential information \*\*\***  
**that should not be released to the public.**

## 1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of NPS Pharmaceuticals' proposed risk evaluation and mitigation strategy (REMS) documents received by FDA on January 21, 2015 (via email). This amendment includes all REMS documents. In addition, this review includes revisions to the REMS documents resulting from recent modifications to the Natpara product label and addresses comments provided by the Office of Prescription Drug Promotion (OPDP).

*Impact of Recent Revisions to the Product Label.* The following changes to the label resulted in additional revisions of the REMS documents:

- Label Warning & Precautions, section 5.1 – Added text: “Instruct patients to promptly report clinical symptoms (e.g., persistent localized pain) and signs (e.g., soft tissue mass tender to palpation) that could be consistent with osteosarcoma.”
- Label Medication Guide – Added text: “Tell your doctor right away if you have pain in any areas of your body that does not go away, or any new or unusual lumps or swelling under your skin that is tender to touch. These are some of the signs and symptoms of osteosarcoma and your doctor may need to do further tests.”

On January 21, 2015 FDA contacted NPS via email requesting a revision of the Natpara REMS document to include the following:

A. Message for Patients: (add to REMS Message Map for Patients, Natpara Patient-Prescriber Acknowledgement Form, and Natpara Patient Brochure)

1. Tell your doctor right away if you have of the following signs or symptoms. These may be signs or symptoms of osteosarcoma:
  - pain in any areas of your body that does not go away.
  - any new or unusual lumps or swelling under your skin that is tender to touch.
2. For the Natpara Patient-Prescriber Acknowledgement Form – add a third bullet under the patient acknowledgement:

-  (b) (4)
  - pain in any areas of  body that does not go away.
  - any new or unusual lumps or swelling under  skin that is tender to touch.

3. For the Natpara Patient Brochure, make it a separate question:

**What are the signs and symptoms of bone cancer?**

- pain in any areas of your body that does not go away.
- any new or unusual lumps or swelling under your skin that is tender to touch.

Tell your doctor right away if you have any of these signs or symptoms.

B. Message for Prescribers: (add to REMS Message Map for Prescribers and to all materials for prescribers)

“Tell your patients to promptly report signs and symptoms of possible osteosarcoma such as persistent localized pain or occurrence of a new soft tissue mass that is tender to palpation.”

## 2 MATERIALS REVIEWED

### 2.1 INFORMATION SOURCES

- Amarilys Vega, MD, MPH/ Kate Oswell, MA, REMS Review for Natpara, dated June 19, 2014.
- Amarilys Vega, MD, MPH/ Kate Oswell, MA, REMS Review for Natpara, dated December 12, 2014.
- Amarilys Vega, MD, MPH/ Kate Oswell, MA, REMS Review for Natpara, dated December 23, 2014.
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- NPS proposed REMS for Natpara amended submission (email), dated January 21, 2015.
- Kendra Jones, OPDP REMS Consult Review, signed in DARRTS on January 16, 2015

## 3 REVIEW RESULTS

Review findings are included in sections 5 and 6 of this review.

## 4 CONCLUSIONS AND RECOMMENDATIONS

The Natpara REMS proposal submitted by NPS on January 21, 2015 requires additional revisions, including revisions to the REMS Document, all REMS appended materials, and REMS Supporting Document. See list of comments included in sections 5 and 6 of this review.

## 5 COMMENTS TO REVIEW DIVISION

DRISK notes that OPDP provided the following comments:

### 5.1 PRESCRIBER TRAINING MODULE AND PHARMACY REPRESENTATIVE TRAINING MODULE

- “What is the approved indication statement for NATPARA?”
  - OPDP is concerned that this section of this presentation implies that this is the full indication for Natpara; however, it omits material information from the full indication, which includes the limitations of use for Natpara. OPDP recommends revising this presentation to also communicate the full indication, which includes the limitations of use for Natpara.

**DRISK response:** DRISK has considered OPDP’s recommendation. The full indication, including limitations of use, is content covered in these training modules. This question is asked as part of the Knowledge Assessment sections of these training modules. Including the full indication, with all limitations of use as an answer to this question, would tip the prescribers and pharmacists off to the correct answer. After further discussion with OPDP, they understand DRISK’s rationale for not including the full limitations of use in the answer to this question.

## 5.2 PRESCRIBER ENROLLMENT FORM

- “I understand that NATPARA is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.”
  - OPDP is concerned that the section of this statement omits material information from the full indication, which includes the limitations of use for Natpara. OPDP recommends revising this presentation to also communicate the *full* indication, which includes the limitations of use for Natpara.

**DRISK Response:** DRISK has considered OPDP’s comment. DRISK has made revisions to the Prescriber Enrollment Form to include the indication and the limitation of use that relates to the REMS program. However, we did not include the limitations of use that do not relate to the risk the Natpara REMS program is in place to mitigate. The full indication, including all limitations of use is included in the mandatory prescriber training module. After further discussion with OPDP, they understand DRISK’s rationale for not including all limitations of use in the form.

## 5.3 PRESCRIBER ENROLLMENT FORM AND REMS WEBPAGE (HOMEPAGE)

- OPDP is concerned that this REMS material fails to communicate pertinent information regarding the appropriate patient selection. Specifically, the REMS material fails to communicate pertinent information from the Boxed Warning that states, “**Avoid use of NATPARA in patients who are at increased baseline risk for osteosarcoma (including those with Paget’s disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, patients with hereditary disorders predisposing to osteosarcoma or patients with a history of prior external beam or implant radiation therapy involving the skeleton)**” (bolded emphasis original)

**DRISK Response:** DRISK has considered OPDP’s comment. However, we feel the complete risk messages are adequately addressed in the REMS training materials for prescribers. As this REMS program has a requirement for mandatory training, including successfully completing a Knowledge Assessment to become certified in the REMS program, we do not believe that shortening the risk message from a communications perspective in the other materials will minimize the overall risk concept to REMS participants. After further discussion with OPDP, they understand DRISK’s rationale for not including this information in these communications.

## 5.4 REMS WEBPAGE (HOMEPAGE)

- “NATPARA is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.”
  - OPDP is concerned that this presentation omits material information from the full indication, which includes the limitations of use for Natpara. OPDP recommends revising this presentation section of these REMS materials to also communicate the full indication, which includes the limitations of use for Natpara.

**DRISK Response:** DRISK has considered OPDP’s comment. The web page was revised to include the indication and the limitation of use that relates to the REMS program. However, we did not include the limitations of use that do not relate to any risks the Natpara REMS program is

in place to mitigate. After further discussion with OPDP, they understand DRISK's rationale for not including all limitations of use on the webpage.

## 5.5 PATIENT BROCHURE AND PATIENT-PRESCRIBER ACKNOWLEDGEMENT FORM

- [REDACTED] (b) (4)
- OPDP is concerned that this presentation omits material information from the full indication, which includes the limitations of use for Natpara. OPDP recommends revising this presentation section of these REMS materials to also communicate the *full* indication, which includes the limitations of use for Natpara in consumer-friendly language. The “**What is NATPARA?**” (bolded emphasis original) section of the draft Medication Guide states the following:
  - NATPARA is a prescription parathyroid hormone (PTHHT) used with calcium and vitamin D [REDACTED] (b) (4) to control low blood calcium (hypocalcemia) in people with low PTHHT blood levels (hypoparathyroidism).
  - NATPARA is only for people who do not respond well to treatment with calcium and active forms of vitamin D alone, because it may increase the possible risk of bone cancer (osteosarcoma).
  - NATPARA was not studied in people with hypoparathyroidism caused by calcium sensing receptor mutations.
  - NATPARA was not studied in people who get sudden hypoparathyroidism after surgery.

**DRISK Response:** DRISK has considered OPDP's comment. We have revised the patient materials based on the language from the Medication Guide, however, we did not include the limitations of use that do not relate to any risks the Natpara REMS program is in place to mitigate. After further discussion with OPDP, they understand DRISK's rationale.

- [REDACTED] (b) (4)
- OPDP is concerned that the overall presentation of the heading [REDACTED] (b) (4) is promotional in tone. OPDP recommends deleting the statement [REDACTED] (b) (4)

**DRISK Response:** DRISK and DMEP discussed whether to include the statement [REDACTED] (b) (4). This statement is supported by the data included in Section 14 of the Prescribing Information. DMEP and DRISK determined that this is not an overreaching statement and recommend to retain this sentence in the patient materials so that a benefit:risk conversation can take place between the patient and prescriber.

## **6 COMMENTS FOR THE APPLICANT**

1. FDA acknowledges receiving on January 21, 2015 your amendment of the Natpara REMS.
2. The Natpara REMS proposal submitted by NPS on January 21, 2015 requires additional revisions. The following table lists all FDA comments and recommendations. In addition, copies of all REMS documents with tracked changes are appended.

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## **Appended Materials**

Appendix 1 – Natpara REMS Document

Appendix 2 – Natpara REMS Training Module for Prescribers

Appendix 3 – Natpara REMS Prescriber Enrollment Form

Appendix 4 – Natpara REMS Program: An Introduction

Appendix 5 – Natpara REMS Training Module for Pharmacy Representatives

Appendix 6 – Natpara REMS Pharmacy Enrollment Form

Appendix 7 – Natpara Patient Brochure

Appendix 8 – Natpara REMS Patient-Prescriber Acknowledgement Form

Appendix 9 – Natpara REMS Website – Prescriber Certification Webpage

Appendix 10 – Natpara REMS Website – Pharmacy Certification Webpage

Appendix 11 – Natpara REMS Website – Home

Appendix 12 – REMS Supporting Document

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/s/  
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AMARILYS VEGA  
01/23/2015

CYNTHIA L LACIVITA  
01/23/2015  
Concur

# Internal Consult

\*\*\*\*Pre-decisional Agency Information\*\*\*\*

**Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.**

To: Joyce Weaver, Senior Risk Management Analyst, DRISK

From: Kendra Y. Jones, Regulatory Review Officer

CC: Kendra Y. Jones, Regulatory Review Officer, OPDP  
Adora Ndu, Team Leader, OPDP  
Terrolyn Thomas, SRPM, OSE  
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Kate Heinrich Oswell, Health Communications Analyst, DRISK  
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CDER-OPDP-RPM  
Michael Wade, RPM, OPDP

Date: January 16, 2015

Re: BLA # 125511  
NATPARA<sup>®</sup> (parathyroid hormone, human) for injection,  
for subcutaneous use (Natpara)  
Comments on draft Risk Evaluation and Mitigation Strategies (REMS)  
Materials (Submission date: January 8, 2015)

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## **Materials Reviewed**

OPDP has reviewed the following proposed REMS materials for NATPARA:

- Healthcare Provider (HCP) REMS Materials:

- Letter to Prescribers
  - Prescriber Training Module
  - Prescriber Enrollment Form
  - REMS Program – An Introduction
  - Pharmacy Representative Training Module
  - Pharmacy Enrollment Form
  - REMS Webpage
  - Prescriber Certification Webpage
  - Pharmacy Certification Webpage
- Direct-to-Consumer (Patient) REMS Materials:
    - Patient Brochure
  - Healthcare Provider (HCP) and Patient REMS Material:
    - Patient-Prescriber Acknowledgement Form

The version of the draft REMS materials used in this review were emailed by Kate Heinrich Oswell on January 9, 2015, and is attached to the end of this review.

The version of the proposed draft PI that was used for this review was obtained from Elizabeth Chen on January 13, 2014.

OPDP offers the following comments on these draft REMS materials for Natpara.

### **General Comments**

Please remind NPS Pharmaceuticals (NPS) that REMS materials are not appropriate for use in a promotional manner.

OPDP notes that the Natpara PI is still being reviewed and modified. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved PI.

OPDP cannot comment on place holders such as “www.NATPARAREMS.com.” However, we recommend that this item represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind NPS that the REMS specific website should not be the sole source of approved REMS materials.

### **REMS Materials**

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- Healthcare Provider (HCP) REMS Materials:
  - Letter to Prescribers
  - Prescriber Training Module

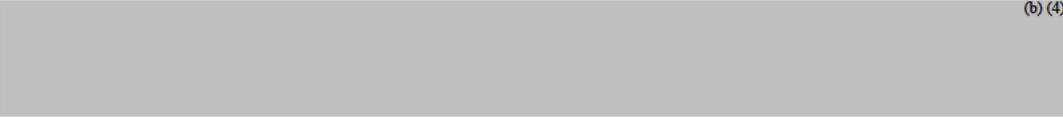
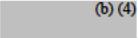
- Prescriber Enrollment Form
  - REMS Program – An Introduction
  - Pharmacy Representative Training Module
  - Pharmacy Enrollment Form
  - REMS Webpage
  - Prescriber Certification Webpage
  - Pharmacy Certification Webpage
- Direct-to-Consumer (Patient) REMS Materials:
    - Patient Brochure
  - Healthcare Provider (HCP) and Patient REMS Material:
    - Patient-Prescriber Acknowledgement Form

### **Specific Comments**

OPDP considers the following statements promotional in tone and recommends revising or deleting them from the REMS pieces:

- **Letters for Prescribers**
  - OPDP is concerned that the section of this REMS material entitled “**Indication**” (bolded emphasis original) implies that this is the full indication for Natpara; however, it omits material information from the full indication, which includes the limitations of use for Natpara. OPDP recommends revising the “**Indication**” (bolded emphasis original) section of this REMS material to also communicate the **full** indication, which includes the limitations of use for Natpara.
  - OPDP is concerned that this REMS material fails to communicate important information regarding the goals of the Natpara REMS. Specifically, the draft supporting document states, “NATPARA is not a parathyroid hormone replacement.” OPDP recommends revising this REMS material to include pertinent information consistent with the goals of the REMS.
  - “Prescribers must counsel patients and submit signed NATPARA *REMS Patient-Prescriber Acknowledgement Form* prior to initiation of therapy.” (italicized emphasis original)
    - OPDP is concerned that this REMS material fails to explicitly inform prescribers about the information that patients should be counseled on prior to initiating therapy. For example, the draft supporting document states, [REDACTED] (b) (4) OPDP recommends revising this REMS material to inform prescribers

about the information they should counsel their patients on prior to initiating Natpara.

- OPDP is concerned that this REMS material includes some information regarding the indication for Natpara; however, it fails to communicate additional pertinent information regarding the appropriate patient selection. Specifically, the REMS material fails to communicate pertinent information from the Boxed Warning that states, **“Because of the potential risk of osteosarcoma, prescribe NATPARA only to patients who cannot be well- controlled on calcium and active forms of vitamin D and for whom the potential benefits are considered to outweigh the potential risk... Avoid use of NATPARA in patients who are at increased baseline risk for osteosarcoma (including those with Paget’s disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, patients with hereditary disorders predisposing to osteosarcoma or patients with a history of prior external beam or implant radiation therapy involving the skeleton)”** (bolded emphasis original)
- **Prescriber Training Module, and Pharmacy Representative Training Module**
  - “Due to the potential risk of osteosarcoma, NATPARA is only recommended for patients who cannot be well-controlled on calcium and active forms of vitamin D alone”
    - OPDP is concerned that this statement omits material information from the Boxed Warning section of the draft Natpara PI that states, **“Because of the potential risk of osteosarcoma, prescribe NATPARA only to patients who cannot be well- controlled on calcium and active forms of vitamin D and for whom the potential benefits are considered to outweigh the potential risk.”** (bolded emphasis original; underlined emphasis added)
  -  (b) (4)
    - OPDP is concerned that the overall presentation of the subheading  (b) (4) in conjunction with the statement,  (b) (4) is promotional in tone. OPDP recommends deleting this presentation from these REMS material.
  - “What is the approved indication statement for NATPARA?”
    - OPDP is concerned that the section of this presentation of the implies that this is the full indication for Natpara; however, it omits material information from the full indication, which includes the

limitations of use for Natpara. OPDP recommends revising this presentation to also communicate the **full** indication, which includes the limitations of use for Natpara.

- **Prescriber Enrollment Form**

- “I understand that NATPARA is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.”
  - OPDP is concerned that the section of this statement omits material information from the full indication, which includes the limitations of use for Natpara. OPDP recommends revising this presentation to also communicate the **full** indication, which includes the limitations of use for Natpara.
- “I understand that there is a potential risk of osteosarcoma associated with NATPARA.”
  - OPDP is concerned that this REMS material omits material information from the Boxed Warning that states, “... **In male and female rats, NATPARA caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration.**” (bolded emphasis original; underlined emphasis added)
- OPDP is concerned that this REMS material fails to communicate important information regarding the goals of the Natpara REMS. Specifically, the draft supporting document states, “NATPARA is not a parathyroid hormone replacement.” OPDP recommends revising this REMS material to include pertinent information consistent with the goals of the REMS.
- OPDP is concerned that this REMS material includes some information regarding the indication for Natpara; however, it fails to communicate additional pertinent information regarding the appropriate patient selection. Specifically, the REMS material fails to communicate pertinent information from the Boxed Warning that states, “**Because of the potential risk of osteosarcoma, prescribe NATPARA only to patients who cannot be well- controlled on calcium and active forms of vitamin D and for whom the potential benefits are considered to outweigh the potential risk... Avoid use of NATPARA in patients who are at increased baseline risk for osteosarcoma (including those with Paget’s disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, patients with hereditary disorders predisposing to osteosarcoma or patients with a history of prior external beam or implant radiation therapy involving the skeleton)**” (bolded emphasis original)

- **REMS Webpage**

- OPDP is concerned that this REMS material fails to communicate pertinent information regarding the appropriate patient selection. Specifically, the REMS material fails to communicate pertinent information from the Boxed Warning that states, **“Avoid use of NATPARA in patients who are at increased baseline risk for osteosarcoma (including those with Paget’s disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, patients with hereditary disorders predisposing to osteosarcoma or patients with a history of prior external beam or implant radiation therapy involving the skeleton)”** (bolded emphasis original)
- “NATPARA is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.”
  - OPDP is concerned that this presentation omits material information from the full indication, which includes the limitations of use for Natpara. OPDP recommends revising this presentation section of these REMS materials to also communicate the **full** indication, which includes the limitations of use for Natpara in consumer-friendly language.
- “Because of the potential risk of osteosarcoma, NATPARA is only recommended for patients who cannot be well-controlled on calcium and active forms of vitamin D alone”
  - OPDP is concerned that this statement omits material information from the Boxed Warning section of the draft Natpara PI that states, **“Because of the potential risk of osteosarcoma, prescribe NATPARA only to patients who cannot be well- controlled on calcium and active forms of vitamin D and for whom the potential benefits are considered to outweigh the potential risk.”** (bolded emphasis original; underlined emphasis added)

- **Patient Brochure**

- **“Natpara Patient Brochure**

...

What you need to know about NATPARA?” (bolded emphasis original)

- OPDP is concerned that the heading “What you need to know about NATPARA” as presented in this draft implies that the REMS material will provide a more comprehensive presentation of all of

information patients need to know about Natpara; however, the this REMS material only discloses some risk information from the draft PI regarding the potential risk of osteosarcoma, the Natpara REMS program, and some information regarding the indication. OPDP recommends revising the heading “What you need to know about NATPARA” to more accurately communicate the risk information that is conveyed in this REMS material.

○ [REDACTED] (b) (4)

- OPDP is concerned that this presentation omits material information from the full indication, which includes the limitations of use for Natpara. OPDP recommends revising this presentation section of these REMS materials to also communicate the **full** indication, which includes the limitations of use for Natpara *in consumer-friendly language*. The “**What is NATPARA?**” (bolded emphasis original) section of the draft Medication Guide states the following :

- NATPARA is a prescription parathyroid hormone (PTHHT) used with calcium and vitamin D or as a substitute for calcium and active forms of vitamin D to control low blood calcium (hypocalcemia) in people with low PTHHT blood levels (hypoparathyroidism).

- NATPARA is only for people who do not respond well to treatment with calcium and active forms of vitamin D alone, because it may increase the possible risk of bone cancer (osteosarcoma).

- NATPARA was not studied in people with hypoparathyroidism caused by calcium sensing receptor mutations.

- NATPARA was not studied in people who get sudden hypoparathyroidism after surgery.

○ [REDACTED] (b) (4)

- OPDP is concerned that this statement is promotional in tone. OPDP recommends deleting this statement.

○ **“What is the serious risk of NATPARA?”**

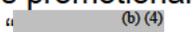
- Possible risk of bone cancer.
- During drug testing, the medicine in NATPARA caused some rats to develop bone cancer called osteosarcoma. In people, osteosarcoma is a serious but rare cancer.” (bolded emphasis original)

- OPDP is concerned that this statement implies that this section will provide a more comprehensive presentation of all of the risks associated with the drug; however, this section only discloses some risk information from the draft PI regarding the potential risk of osteosarcoma. OPDP recommends revising this statement to more accurately communicate the limited REMS associated risk information that is conveyed in this section. Additionally, OPDP recommends revising this REMS material to include a directive on how to obtain the product labeling for Natpara, which includes the PI and Medication Guide.

- **Patient-Prescriber Acknowledgement Form**

- 



- OPDP is concerned that this presentation omits material information from the full indication, which includes the limitations of use for Natpara. OPDP recommends revising this presentation section of these REMS materials to also communicate the **full** indication, which includes the limitations of use for Natpara in consumer-friendly language. OPDP is concerned that the overall presentation of the heading "**Benefits**" (bolded emphasis original) in conjunction with the statement,  (b) (4) is promotional in tone. OPDP recommends deleting the statement " (b) (4)

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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KENDRA Y JONES  
01/16/2015

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: January 16, 2015

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer  
Division of Risk Management (DRISK)  
Kate Oswell, MA, Health Communications Analyst, DRISK

DRISK Team Leader: Naomi Redd, Pharm D, Acting Team Leader, DRISK

Division Director: Cynthia LaCivita, Pharm.D, Acting Director DRISK

Subject: Evaluation of REMS Documents submitted via email on January 8, 2015

Drug Name(s): Natpara<sup>®</sup>, recombinant Human Parathyroid Hormone [rhPTH (1-84)] for injection

Therapeutic Class: Parathyroid hormone

Dosage and Route: 25 mcg, 50 mcg, 75 mcg, and 100 mcg; subcutaneous injection

Application Type/Number: BLA 125511

Submission Number: email submission from January 8, 2015

Applicant/sponsor: NPS Pharmaceuticals

OSE RCM #: 2013-2500 and 2013-2496

**\*\*\* This document contains proprietary and confidential information \*\*\*  
that should not be released to the public.**

## **1 INTRODUCTION**

This review documents the Division of Risk Management's (DRISK) evaluation of NPS Pharmaceuticals' proposed risk evaluation and mitigation strategy (REMS) documents received by FDA on January 8, 2015 (via email). This amendment includes all REMS documents, some of which have not been previously submitted to FDA.

## **2 MATERIALS REVIEWED**

### **2.1 INFORMATION SOURCES**

- Amariyls Vega, MD, MPH, REMS Review for Natpara, dated June 19, 2014.
- Amariyls Vega, MD, MPH, REMS Review for Natpara, dated December 12, 2014.
- Amariyls Vega, MD, MPH, REMS Review for Natpara, dated December 23, 2014.
- NPS proposed REMS for Natpara amended submission (email), dated January 8, 2015.

## **3 REVIEW RESULTS**

Review findings are included in section 5 of this review.

## **4 CONCLUSIONS AND RECOMMENDATIONS**

The Natpara REMS proposal submitted by NPS on January 8, 2015 requires numerous revisions, including revisions to the REMS Document, all REMS appended materials, and REMS Supporting Document. See list of comments included in section 5 of this review.

## **5 COMMENTS FOR THE APPLICANT**

1. FDA acknowledges receiving on January 8, 2015 your amendment of the Natpara REMS.
2. The Natpara REMS proposal submitted by NPS on January 8, 2015 requires numerous revisions. The following table lists all FDA comments and recommendations. In addition, copies of all REMS documents with tracked changes are appended.

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AMARILYS VEGA  
01/16/2015

CYNTHIA L LACIVITA  
01/16/2015  
Concur

**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**  
**Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: December 23, 2014

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer  
Division of Risk Management (DRISK)  
Anahita Tavakoli, MA, Health Communications Analyst, DRISK

DRISK Team Leader: Naomi Redd, Pharm D, Acting Team Leader, DRISK

Division Director: Cynthia LaCivita, Pharm.D, Acting Director DRISK

Subject: Evaluation of proposed REMS Document and Patient-Prescriber Acknowledgement Form

Drug Name(s): Natpara<sup>®</sup>, recombinant Human Parathyroid Hormone [rhPTH (1-84)] for injection

Therapeutic Class: Parathyroid hormone

Dosage and Route: 25 mcg, 50 mcg, 75 mcg, and 100 mcg; subcutaneous injection

Application Type/Number: BLA 125511

Submission Number: Sequence No. 0047

Applicant/sponsor: NPS Pharmaceuticals

OSE RCM #: 2013-2500 and 2013-2496

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## **1 INTRODUCTION**

This review documents the Division of Risk Management's (DRISK) evaluation of NPS Pharmaceuticals' proposed risk evaluation and mitigation strategy (REMS) document received by FDA on November 6, 2014 (Seq. No. 0047) and proposed Natpara REMS Patient-Prescriber Acknowledgement Form received by FDA via email on December 22, 2014.

## **2 MATERIALS REVIEWED**

### **2.1 INFORMATION SOURCES**

- Amariyls Vega, MD, MPH, REMS Review for Natpara, dated June 19, 2014.
- Amariyls Vega, MD, MPH, REMS Review for Natpara, dated December 12, 2014.
- NPS proposed REMS for Natpara amended submission, dated November 6, 2014.
- Natpara REMS Patient-Prescriber Acknowledgement Form, received December 22, 2014.

## **3 REVIEW RESULTS**

The Natpara REMS proposal submitted by NPS on November 6, 2014 requires numerous revisions to include REMS tools FDA deems necessary to maintain the benefit:risk balance for Natpara. DRISK developed a draft REMS Assessment Plan for Natpara to assist the sponsor in the development of the Natpara REMS Program.

NPS Pharmaceuticals proposed Patient-Prescriber Acknowledgement Form also requires multiple revisions to harmonize it with the revised REMS Document.

## **4 CONCLUSIONS AND RECOMMENDATIONS**

The proposed REMS document and Patient-Prescriber Acknowledgement Forms require multiple revisions.

DRISK recommends DMEP send NPS Pharmaceuticals all comments included in section 5 of this review, including the REMS materials in appendices 1-3.

## **5 COMMENTS FOR THE APPLICANT**

1. FDA acknowledges receiving on November 6, 2014 your proposal for Natpara REMS and a proposal for the Natpara REMS Patient-Prescriber Acknowledgement Form received via email on December 22, 2014.
2. The Natpara REMS proposal submitted by NPS on November 6, 2014 requires numerous revisions. To facilitate the review process, FDA is providing a clean copy of the draft REMS for Natpara which includes all FDA-proposed revisions to the REMS document submitted by NPS on November 6. See appendix 1. For subsequent submissions, FDA requests that, in addition to providing a tracked changes version of the REMS document included in appendix 1, NPS summarizes in table format all changes the company proposes and the rationale for these (see below).

3. A revised version of the Natpara REMS Patient-Prescriber Acknowledgement Form is included in Appendix 2.
4. A draft REMS Assessment Plan for Natpara is included in appendix 3.
5. Additional comments
  - a. Education or communication provided as part of a REMS should emphasize the safety messages important for the safe use of the product.
  - b. Product marketing materials generally are not appropriate to educate about product risks.
  - c. When addressing comments from FDA reviewers, in addition to tracking changes in the REMS documents, please provide a summary table in MS Word listing all revisions proposed by NPS to REMS documents and rationale for the change. (See example provided below).

<b>Natpara REMS: Summary of Changes</b>	
<b>NPS revisions/comments mm/dd/yyyy</b>	<b>FDA revisions/comments mm/dd/yyyy</b>
Global/General comments	
<i>Comment</i>	
<i>Comment</i>	
REMS Document	
<i>Comment</i>	
<i>Comment</i>	
REMS Letter for Prescribers	
<i>Comment</i>	
<i>Comment</i>	
REMS Letter for Pharmacies	
<i>Comment</i>	
<i>Comment</i>	
REMS Letter for Professional Societies	
<i>Comment</i>	
<i>Comment</i>	
Training Module for Prescribers	
<i>Comment</i>	
<i>Comment</i>	
Training Module for Pharmacy Representatives	
<i>Comment</i>	
<i>Comment</i>	
Prescriber Enrollment Form	
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Pharmacy Enrollment Form	
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<i>Comment</i>	
Patient Brochure	
<i>Comment</i>	

<i>Comment</i>	
Patient-Prescriber Acknowledgement Form	
<i>Comment</i>	
<i>Comment</i>	
REMS Website (landing page)	
<i>Comment</i>	
<i>Comment</i>	

Appended Materials

Appendix 1 – Natpara REMS Document

Appendix 2 – Natpara REMS Patient-Prescriber Acknowledgement Form

Appendix 3 – Draft REMS Assessment Plan

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12/23/2014

CYNTHIA L LACIVITA  
12/28/2014  
Concur

**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**  
**Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: December 12, 2014

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer  
Division of Risk Management (DRISK)  
Kate Oswell, MA, Health Communications Analyst, DRISK

DRISK Team Leader: Naomi Redd, Pharm D, Acting Team Leader, DRISK  
Doris Auth, Pharm D, Acting Team Leader, DRISK

Division Director Cynthia LaCivita, Pharm.D, Acting Director DRISK

Subject: Evaluation of need for a REMS

Drug Name(s): Natpara<sup>®</sup>, recombinant Human Parathyroid Hormone [rhPTH (1-84)] for injection

Therapeutic Class: Parathyroid hormone

Dosage and Route: 25 mcg, 50 mcg, 75 mcg, and 100 mcg; subcutaneous injection

Application Type/Number: BLA 125511

Submission Number: Sequence No.0000 and 0011

Applicant/sponsor: NPS Pharmaceuticals

OSE RCM #: 2013-2500 and 2013-2496

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## **EXECUTIVE SUMMARY**

This review documents the Division of Risk Management's (DRISK) evaluation of whether a risk evaluation and mitigation strategy (REMS) is necessary for Natpara (recombinant human parathyroid hormone [rhPTH (1-84)] for injection, BLA 125511). On November 6, 2014, the sponsor amended their submission to include a REMS proposal to manage the risk of osteosarcoma associated to Natpara.

Hypoparathyroidism is a serious disease with no currently available hormone replacement therapy. If left untreated or inadequately treated, hypoparathyroidism will result in clinically significant and serious adverse effects. There is a medical need for new treatments for hypoparathyroidism as the current standard of care does not address all physiologic aspects of hypoparathyroidism and is burdensome for certain patients who are required to ingest large and frequent doses of calcium and vitamin D. The active ingredient in Natpara is identical to the human amino acid protein and has been developed for the treatment of hypoparathyroidism.

The clinical efficacy demonstrated for Natpara, in context with the potential risk of osteosarcoma, has a benefit:risk profile that does not support the indication proposed by the sponsor (i.e., use for the general population of patients with hypoparathyroidism). Instead, the indication for Natpara was revised to, "as an adjunct to a regimen of calcium and Vitamin D to control hypocalcemia in patients with hypoparathyroidism." In addition, if approved, the product label will include the following limitation of use, "Because of the potential risk of osteosarcoma, Natpara is recommended only for patients who cannot be well-controlled on calcium and active forms of vitamin D alone."

The safe use of Natpara requires prescribers' and patients' understanding of complex efficacy and safety messages, the assurance that only prescribers knowledgeable about the appropriate use of Natpara are able to prescribe the drug, and that patients have the opportunity to weigh the potential benefits and risks prior to initiation of therapy. The extent of communication and safe use assurances required for Natpara cannot be achieved through labeling alone or in combination with a REMS with a Medication Guide and a communication plan. Natpara requires a REMS with elements to assure safe use (ETASU) to maintain this product's benefit:risk balance. The proposed REMS includes prescriber certification, pharmacy certification and documentation of a safe use condition.

## **1 INTRODUCTION**

This review documents the Division of Risk Management's (DRISK) evaluation of whether a risk evaluation and mitigation strategy (REMS) is necessary for Natpara (recombinant human parathyroid hormone [rhPTH(1-84)] for injection, BLA 125511). Also included is the sponsor's proposed REMS and the Agency's proposed REMS that contain the minimum necessary elements to mitigate the risk of osteosarcoma associated to Natpara.

DRISK deferred comments regarding the need for a REMS prior to the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting held on September 12, 2014 because the Division of Metabolism and Endocrinology Products (DMEP) had not made a final determination regarding the benefit:risk balance for Natpara (see DRISK's review dated June 19, 2014).

The EMDAC meeting was held on September 12, 2014 to discuss the efficacy and safety of Natpara. The majority of EMDAC panel members concluded that Natpara demonstrated the ability to reduce patients' daily calcium and vitamin D requirements but expressed uncertainty about the extent to which Natpara addresses actual clinical need in patients. In addition, EMDAC panel members expressed a high level of concern regarding the risk of osteosarcoma and recommended that there be some effort to mitigate the risk. A REMS proposal based on DMEP's final determination of the benefit:risk profile of Natpara was discussed with members of the REMS Oversight Committee (ROC) meeting on October 8, 2014. Members of the ROC supported DMEP/DRISK's proposal to require a REMS with elements to assure safe use (ETASU) to ensure the benefits outweigh the risks for Natpara.

## **2 MATERIALS REVIEWED**

### **2.1 INFORMATION SOURCES**

- Amarilys Vega, MD, MPH, REMS Review for Natpara, dated June 19, 2014.
- Natpara Advisory Committee meeting slide presentations – FDA and NPS Pharmaceuticals, dated September 12, 2014
- REMS Oversight Committee briefing documents and meeting minutes dated October 8, 2014.
- NPS proposed REMS for Natpara amended submission, dated November 6, 2014.

## **3 ANALYSIS OF NEED FOR A REMS**

This section includes the analysis of the need for a REMS.

### **3.1 BENEFIT:RISK ASSESSMENT**

#### **3.1.1 Rationale for Drug Development**

*Hypoparathyroidism is a serious disease with no currently available hormone replacement therapy. If left untreated or inadequately treated, hypoparathyroidism will result in clinically significant and serious adverse effects. There is a medical need for new treatments for hypoparathyroidism as the current standard of care does not address all physiologic aspects of hypoparathyroidism and is burdensome for certain patients who are required to ingest large and frequent doses of calcium and vitamin D. The active ingredient in Natpara is identical to the human amino acid protein and has been developed for the treatment of hypoparathyroidism.*

NPS Pharmaceuticals is seeking approval for Natpara as replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism. The active pharmaceutical ingredient in Natpara (rhPTH(1-84)), is identical to the human amino acid protein and has been developed for the treatment of hypoparathyroidism and for the treatment of osteoporosis. This product, rhPTH(1-84), is not approved in the US but was granted marketing authorization on April 24, 2006 in the European Union for the treatment of osteoporosis in postmenopausal women at high risk of fractures. In 2007, Natpara was granted an orphan designation for the treatment of hypoparathyroidism.

Hypoparathyroidism is a serious but rare disease that results from deficiency or absence of parathyroid hormone (PTH); it is estimated to affect approximately 60,000 patients.

Hypoparathyroidism results most commonly (70-80% of cases) as a postoperative sequelae of thyroid, parathyroid, or other neck surgery. Untreated or inadequately treated, hypoparathyroidism leads to clinically significant metabolic sequelae including hypocalcemia. Hypoparathyroidism is characterized by low circulating PTH levels in association with hypocalcemia, hypercalciuria, hyperphosphatemia, and hypophosphaturia.

Classic symptoms are primarily related to neuromuscular irritability as a result of hypocalcemia (e.g., numbness, paresthesias, tetany, seizures, laryngospasm, and cardiac arrhythmias). Neurological manifestations of hypocalcemia include symptoms such as difficulty in concentrating (“brain fog”), effects on mood and ideation, insomnia, and fatigue.

Chronic PTH deficiency results in chronic hypocalcemia (may lead to cardiomyopathy), chronic hyperphosphatemia (may lead to precipitation of calcium phosphate in soft tissues), chronic hypercalciuria (may lead to nephrocalcinosis, nephrolithiasis, and progressive renal failure), low bone turnover state, and increased bone mass (may be associated with poor bone quality and increased risk of fractures).

There is a medical need for new treatments for hypoparathyroidism. There is no approved PTH replacement product; the current management consists of pharmacological doses of calcium and active vitamin D to manage hypocalcemia. However, chronic use of pharmacological doses of calcium and active vitamin D can be burdensome to patients (may require large number of calcium and vitamin D pill and/or frequent dosing) and may be associated with hypercalcemia and calcifications on the kidney, brain, and other soft tissues. In addition, calcium and vitamin D replacement therapy does not address other physiologic aspects of hypoparathyroidism including lack of endogenous 1,25-dihydroxyvitamin D production, hypercalciuria, hyperphosphatemia, and metabolic bone abnormalities.

### **3.1.2 Efficacy Results**

*The clinical development program did not demonstrate that Natpara is able to fulfill the physiological functions of endogenous parathyroid hormone; however, it demonstrated that Natpara does not provide significant clinical benefits over the standard of care with the exception of a selected group of patients.*

The pivotal trial compared Natpara to a group treated with the standard of care (calcium and vitamin D supplementation) demonstrating that the primary efficacy endpoint was met, i.e., maintenance of serum calcium along with a decreased burden of calcium and vitamin D supplements of at least 50%. For most patients, the reduction in the total daily amount of calcium supplementation did not result in a substantial decrease in the number of supplement doses taken per day (oral calcium reduced from a median of 2,000 mg daily to 750 mg daily). However, for a selected group of patients with hypoparathyroidism who require ingesting large daily doses of calcium and vitamin D, a reduction in the amount of calcium and vitamin D supplements while still maintaining normal calcium levels in blood would be an advantage over current therapy.

When compared to the group receiving the standard of care, patients treated with Natpara did not demonstrate improvements in urinary calcium excretion. FDA reviewers demonstrated through the use of systems pharmacology modeling the feasibility of controlling hypercalciuria by more frequent dosing regimens or by a slow release PTH formulation. Additional studies are required to evaluate the impact that modifications in dosing schedule and/or formulation may have on

urinary calcium excretion. Demonstration of reduction in urinary calcium excretion would represent a significant clinical benefit over the standard of care.

### 3.1.3 Safety Profile

*The anticipated target patient population for Natpara is relatively small, including patients in all age groups. Natpara may be used chronically over a patient's lifetime. Based on nonclinical data, Natpara has a potential risk of osteosarcoma similar to that of Forteo (teriparatide). Osteosarcoma is a life-threatening but rare form of cancer with risk factors likely to be present among patients treated with Natpara. The anticipated Natpara prescriber population include endocrinologists primarily – a group with no particular expertise with osteosarcoma.*

The human relevance of Natpara-induced osteosarcoma in rats is unknown. The impact of long-term use of Natpara, treatment employing different dosing schedules and formulations, and exposure of patients with increased baseline risk on the incidence rate of osteosarcoma in humans has not been determined. Forteo, which has an identical sequence to the 34 N-terminal amino acids of the 84-amino acid human parathyroid hormone, also has a potential risk of osteosarcoma. Postmarketing data has not established a causal association between Forteo and the occurrence of osteosarcoma. The current standard of care for hypoparathyroidism does not have the potential risk of osteosarcoma.

The most important safety concern with Natpara is a potential risk of osteosarcoma. The signal was identified in nonclinical data. Natpara caused a dose- and treatment-dependent increase in the incidence of osteosarcoma in male and female rats. The effect was observed at clinically relevant systemic exposures to Natpara (3 to 71 times the exposure in humans given a 100 µg dose).

Osteosarcoma is a life-threatening but rare type of primary bone cancer. The estimated incidence of osteosarcoma ranges from 1.7 to 4.4 per million depending on age. The majority of cases occur in adolescence with a secondary peak occurring among the elderly (> 60 years). The 5-year survival rate of osteosarcoma is 60-80% in localized lesions and 15-30% in metastatic tumors. Individuals with increased baseline risk for osteosarcoma include those with Paget's disease of bone, open epiphyses (pediatric patients and young adults), or prior external beam or implant radiation therapy involving the skeleton.

Natpara will most likely be prescribed primarily by endocrinologists who understand the management of hypoparathyroidism but may not have a particular expertise with osteosarcoma; thus, the anticipated need to inform prescribers about this potential serious risk. FDA does not anticipate the use of Natpara for indications other than hypoparathyroidism.

Natpara may be used chronically over a patient's lifetime including patients in all age groups and with risk factors for osteosarcoma; therefore, it is important that patients and their healthcare providers become knowledgeable about the risk of osteosarcoma before initiation of therapy. The standard of care for hypothyroidism, i.e., calcium and vitamin D supplementation, do not have the potential risk of osteosarcoma or any other serious risk different from those also associated to Natpara.

It is uncertain how findings from nonclinical studies translate into a human risk of osteosarcoma or how would the long-term use of Natpara, treatment with different dosing schedules and formulations, and exposure to patients with increased baseline risk impact the incidence rate of osteosarcoma in humans. Postmarketing studies are required to elucidate these uncertainties.

### 3.1.4 Other Drugs with a Similar Safety Profile

*Forteo (teriparatide), a recombinant human parathyroid hormone (PTH) analogue (shortened molecule) used for treating osteoporosis, also has a potential risk of osteosarcoma. The carcinogenic activity of Forteo is not discernable from that observed for Natpara. Forteo has a REMS including a communication plan and a Medication Guide. Forteo REMS assessments showed that many prescribers do not read or review REMS-related materials. The Forteo REMS has not met its goal to inform patients about the risk of osteosarcoma.*

Forteo (teriparatide, PTH (1-34), NDA 21318), which has an identical sequence to the 34 N-terminal amino acids of the 84-amino acid human parathyroid hormone, also has a potential risk of osteosarcoma. Forteo is indicated for the treatment of osteoporosis (older patients), and its use is limited to <2 years of therapy due to a lack of data on treatment durations longer than this. Forteo carries a boxed warning for the risk of osteosarcoma and was approved with a REMS which includes a Medication Guide and a communication plan to communicate the risk of osteosarcoma. Nonclinical studies demonstrated that there is no discernable difference between the carcinogenic activity of Forteo and that observed for Natpara. Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period; however, a causal association to the use of Forteo has not been established.

The Forteo prescriber population includes rheumatologists (31%), endocrinologists (38%), internists (14%), family practitioners (11%), Ob-gyn (<1%), orthopedic surgery (3%), and other (3%).<sup>1</sup> The goal of the Forteo REMS is to inform patients and prescribers about the risk of osteosarcoma. Forteo REMS assessments showed that many prescribers do not read or review REMS-related materials (see Table 7 below from Forteo’s 3-year REMS Assessment Report, dated July 2012).

**Table 7. Physician Reporting of Awareness of and Having Read or Reviewed Educational Materials, by Specialty**

Survey Question	Primary Care Physicians n (%)	Targeted Specialists n (%)	Other n (%)
<b>7. For each of the following Forteo educational materials, please check all boxes that apply to you.</b>	n = 53	n = 138	n = 11
<b>Aware of</b>			
Full prescribing information	32 (60%)	98 (71%)	9 (82%)
Medication Guide for patients	41 (77%)	97 (70%)	10 (91%)
Dear Health Care Provider Letter	34 (64%)	85 (62%)	8 (73%)
<b>Read or reviewed</b>			
Full prescribing information	22 (42%)	75 (54%)	7 (64%)
Medication Guide for patients	13 (25%)	54 (39%)	5 (46%)
Dear Health Care Provider Letter	11 (21%)	39 (28%)	4 (36%)

Note: Not all those who checked “received” also checked “aware of.” Percentages may not sum to 100% because the respondent could select more than one option.

Source: Forteo 3-year REMS Assessment Report

<sup>1</sup> Forteo 3 year - REMS assessment report.

Similarly, REMS assessment data from other approved REMS with a communication plan have not demonstrated that communication plans are effective at reaching all prescribers targeted by the REMS (i.e., making all targeted prescribers aware of the REMS materials).<sup>2</sup> Nevertheless, the Forteo REMS achieved its goal of informing prescribers of the risk of osteosarcoma (91% primary care providers, 99% specialists). These findings support the notion that REMS-related risk messages are also communicated to prescribers through sources other than REMS materials. The Forteo REMS has not met its goal to inform patients about the risk of osteosarcoma (70% new users, 51% experienced users new about the risk). Modifications to the Forteo Medication Guide were made recently to address the patient knowledge deficiencies.

### **3.1.5 Advisory Committee Recommendations**

A majority of panel members concluded that Natpara demonstrated the ability to reduce patients' daily calcium and vitamin D requirements but expressed uncertainty about the extent to which Natpara addresses actual physiologic disturbances induced by the disease. Also, a majority of panel members expressed a high level of concern regarding the risk of osteosarcoma and recommended the use of methods beyond labeling to mitigate the risk. The committee voted 8:5 in favor of approval of Natpara.

### **3.1.6 Benefit:Risk Conclusion**

*Natpara has a potential risk of osteosarcoma and does not provide significant clinical benefits over the standard of care with the exception of a selected group of patients. Due to the potential risk of osteosarcoma and the absence of data demonstrating that Natpara addresses the physiologic deficiency of parathyroid hormone, if approved, Natpara will be indicated as an adjunct to a regimen of calcium and Vitamin D for the control of hypocalcemia in patients with hypoparathyroidism. In addition, the product label will include the following limitation of use, "Because of the potential risk of osteosarcoma, Natpara is recommended only for patients who cannot be well-controlled on calcium and active forms of vitamin D alone."*

Based on efficacy findings from the Natpara clinical development program, DMEP has proposed revisions to the indication originally sought by the Applicant (i.e., as replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism). There is a medical need for new treatments for hypoparathyroidism as the current standard of care is burdensome for certain patients with hypoparathyroidism who need to ingest large and frequent doses of calcium and vitamin D. The DMEP proposed revisions to the indication for Natpara is for the control of hypocalcemia as an adjunct to a regimen of calcium and Vitamin D, to control hypocalcemia in patients with hypoparathyroidism. Because of the potential risk of osteosarcoma, Natpara is recommended only for patients who cannot be well-controlled on calcium and active forms of vitamin D alone.

<sup>2</sup> e.g., Prolia, Victoza, Yervoy

### **3.2 RATIONALE FOR THE NEED OF A REMS**

*The safe use of Natpara requires prescribers' and patients' understanding of complex efficacy and safety messages, the assurance that only prescribers knowledgeable about the appropriate use of Natpara are able to prescribe the drug, and that patients have the opportunity to consider the potential benefits and risks prior to initiation of therapy. The extent of communication and safe use assurances required for Natpara cannot be achieved through labeling alone or in combination with a REMS with a medication guide and a communication plan. Therefore, a REMS with elements to assure safe use (ETASU) is necessary to ensure that benefits outweigh the risks of Natpara. The minimum ETASU to ensure that the benefits outweigh the risk for Natpara include: prescriber certification, pharmacy certification, and documentation of safe use condition.*

The management of the risk for osteosarcoma associated with Natpara requires more active risk management methods than those employed by the Forteo REMS. In addition, there are important differences between Forteo and Natpara, i.e., differences in demonstrated efficacy, approved indication and limitations of use, expected duration of use, and anticipated patient and prescriber populations. In addition, Forteo REMS assessment findings suggest that the communication plan REMS approved for Forteo did not reach all prescribers in the targeted population nor was successful at communicating the risk of osteosarcoma to patients (see section 3.1.4 above).

The clinical efficacy demonstrated for Natpara, in context with the potential risk of osteosarcoma, has a benefit:risk profile that does not support the indication proposed by the sponsor (i.e., use for the general population of patients with hypoparathyroidism). Instead, Natpara indication was revised to, "as an adjunct to a regimen of calcium and Vitamin D to control hypocalcemia in patients with hypoparathyroidism." In addition, the product label will include the following limitation of use, "Because of the potential risk of osteosarcoma, Natpara is recommended only for patients who cannot be well-controlled on calcium and active forms of vitamin D alone."

The messages regarding the efficacy and safety of Natpara are complex ones, requiring prescribers to understand the criteria for appropriate patient selection (i.e., Natpara is not intended to be used as parathyroid hormone replacement therapy), have knowledge of the risk factors for osteosarcoma, and understand the imperative of discussing the potential benefits and risks of Natpara with patients and/or their representatives. Patients considering treatment with Natpara must have the opportunity to weigh the potential benefits and risks prior to the initiation of therapy with Natpara.

Natpara will carry a boxed warning for the risk of osteosarcoma; however, based on FDA's experience with risk management programs for other drugs, labeling alone or in combination with a REMS with a Medication Guide and communication plan will not fulfill the need to communicate to all Natpara prescribers and patients the complex benefit and risk messages required for the safe use of this product (see section 3.1.4 above). A REMS with elements to assure safe use (ETASU) is necessary to ensure the benefits outweigh the risk for Natpara.

### **4 RISK MANAGEMENT ACTIVITIES PROPOSED BY THE SPONSOR**

NPS Pharmaceuticals' initial submission on Oct 24, 2013 included a proposed a voluntary Risk Management Plan (RMP). NPS amended their submission on November 6, 2014 to include a proposed REMS that includes elements to assure safe use.

Initially, NPS Pharmaceuticals did not propose a REMS but submitted a RMP to address the risks of hypocalcemia, hypercalcemia, osteosarcoma, and the complexities of Natpara’s injection device. The RMP provided a description of NPS Pharmaceuticals’ commercial support plan and included:

- distribution of Natpara via a restricted specialty pharmacy network;
- healthcare professional and patient training before the product is shipped to the patient;
- healthcare provider and patient support provided by NPS Advantage (NPS support program for patients); and
- a requirement for completion of a referral form to document the patient and physician office staff have been properly trained on the use of Natpara and the delivery device.

Participation by patients and prescribers in the proposed plan is voluntary.

Based on FDA’s assessment of the efficacy and safety of Natpara, a voluntary risk management plan as proposed by the sponsor is insufficient to ensure the safe use of Natpara. See section 3.2 above.

On October 14, 2014, FDA notified NPS via a teleconference that a REMS with elements to assure safe use was necessary to ensure the benefits outweigh the risks for Natpara. Subsequently, on November 6, 2014 the Agency received NPS’s proposed REMS, which includes prescriber certification, specialty pharmacy certification, documentation of safe use condition (prescription authorization form), implementation system, and timetable for submission of REMS assessments.

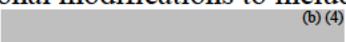
The goals of the Natpara REMS proposed by NPS are the following:

To educate prescribers about:

-  (b) (4)
- 
- 

The REMS proposed by NPS includes the following tools:

-  (b) (4)
- 
- 
- 
- 

**Reviewer’s Comments:** The REMS proposal submitted by NPS on November 6, 2014 is incomplete; it did not include the proposed REMS appended materials or a REMS Supporting Document. The REMS proposed by NPS includes the key elements FDA considers necessary for the Natpara REMS Program. However, it requires additional modifications to include as part of the REMS a Patient-Prescriber Acknowledgement Form  (b) (4)

 a REMS Letter for Prescribers, add the Natpara REMS Program introduction sheet, and to include in the REMS document additional details regarding the

implementation of the Natpara REMS. Section 5 below includes FDA's Natpara REMS proposal.

## **5 DRISK PROPOSED REMS**

The proposed REMS includes prescriber certification, pharmacy certification and documentation of safe use condition (i.e., Patient-Prescriber Agreement Form).

The risk of osteosarcoma associated with Natpara cannot be prevented but can be mitigated by ensuring appropriate prescriber and patient understanding of the benefit:risk balance profile of this product.

The overall burden to the healthcare system of the proposed REMS is limited by the small number of prescribers, and patients impacted by the Natpara REMS. The burden to prescribers consists of the one-time requirement to become certified. The burden to pharmacies and hospital pharmacies consist of having to become a certified pharmacy to participate in the Natpara REMS. Patients and prescribers will be required to sign a Patient-Prescriber Acknowledgement Form. REMS restrictions in the prescribing and dispensing of Natpara may create a barrier to patients' access to the drug, but is necessary to ensure the benefits outweigh the risks of Natpara.

The following sections describe in detail the REMS proposed for Natpara.

### **5.1 GOAL STATEMENT**

The goal of the Natpara REMS is to mitigate the potential risk of osteosarcoma associated with Natpara by:

- a. educating prescribers about the
  - i. potential risk of osteosarcoma associated with the use of Natpara
  - ii. appropriate patient selection
  - iii. safe-use conditions required for prescribing Natpara
- b. informing patients about the potential risk of osteosarcoma associated with the use of Natpara

### **5.2 REMS ELEMENTS**

The proposed Natpara REMS includes the following elements to assure safe use: prescriber certification, pharmacy certification, documentation of safe-use condition, an Implementation System, and a Timetable for Submission of REMS Assessments.

#### **5.2.1 Prescriber Certification**

An ETASU REMS with prescriber and pharmacy certification will ensure that Natpara is prescribed only by certified prescribers (i.e., trained about the risk, appropriate patient selection, the need to inform patients about the risks, and REMS Program requirements). Prescriber certification consists of training and enrollment. To become certified in the Natpara REMS Program, prescribers must:

- review the Prescribing Information for Natpara and the information sheet titled *Natpara REMS Program: An Introduction*,

- complete the *Natpara REMS Training Module for Prescribers*, and
- complete and sign the *Natpara REMS Prescriber Enrollment Form* and submit it to the Natpara REMS Program Coordinating Center.

NPS will establish the Natpara REMS Program Coordinating Center and will send prescribers confirmation of certification.

### 5.2.2 Pharmacy Certification

Pharmacy certification is required to ensure that Natpara is prescribed only by certified prescribers and that Natpara is dispensed only to patients with the required safe-use condition (i.e., completion of the *Natpara REMS Patient-Prescriber Acknowledgement Form*).

To become certified to dispense Natpara, pharmacies must designate a representative. The Pharmacy Representative must:

- review the Prescribing Information for Natpara and the information sheet titled *Natpara REMS Program: An Introduction*,
- complete the *Natpara REMS Training Module for Pharmacy Representatives*, and
- complete and sign the *Natpara REMS Pharmacy Enrollment Form* and submit it to the Natpara REMS Program Coordinating Center.

NPS will need to send confirmation of pharmacy certification to the Pharmacy Representative.

### 5.2.3 Safe-use Condition

Prescriber and pharmacy certification alone does not guarantee that each patient will be informed about the benefits and potential risk for osteosarcoma associated to Natpara. Prescribers will use the *Natpara Patient Brochure* as a counseling tool to assist in the benefit:risk discussion that must take place prior to initiation of treatment with Natpara. The patient and prescriber will complete and sign a *Natpara REMS Patient-Prescriber Acknowledgement Form* documenting the discussion of the benefits and risks associated to Natpara occurred prior to the initiation of therapy. Once completed, the *Natpara REMS Patient-Prescriber Acknowledgement Form* should be sent to the Natpara REMS Program Coordinating Center.

Prior to dispensing Natpara, the pharmacy must verify that the prescriber is certified in the Natpara REMS Program and that a *Natpara REMS Patient-Prescriber Acknowledgement Form* is on record.

## 5.3 NATPARA REMS MESSAGE MAPS FOR PRESCRIBERS, PHARMACY REPRESENTATIVES, AND PATIENTS

The following REMS message maps for prescribers, pharmacy representatives, and patients are based on the current draft product label (December 1, 2014). The message maps contain the key risk messages addressed by the Natpara REMS. The messages included in these maps are consistent (although not necessarily verbatim) with the product label and will be used to guide the development of all REMS-related documents, including REMS assessment survey questions.

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

## 5.4 PROPOSED REMS TOOLS

The proposed Natpara REMS Program will include the following tools:

- *Natpara REMS Letter for Prescribers*
- *Natpara REMS Program: An Introduction*
- *Natpara REMS Training Module for Prescribers*
- *Natpara REMS Training Module for Pharmacy Representatives*
- *Natpara REMS Prescriber Enrollment Form*
- *Natpara REMS Pharmacy Enrollment Form*
- *Natpara Patient Brochure*
- *Natpara REMS Patient-Prescriber Acknowledgement Form*
- *Natpara REMS Website*

## 5.5 REMS ASSESSMENT PLAN

A successful REMS for Natpara will achieve the REMS measurable objectives, will ensure that only certified prescribers prescribe Natpara, that only certified pharmacies dispense Natpara, and that there is documentation of safe use conditions prior to initiation of therapy. A detailed REMS Assessment Plan will be included in forthcoming review in conjunction with the REMS Document.

## 6 CONCLUSIONS AND RECOMMENDATIONS

Natpara requires a REMS with elements to assure safe use (ETASU) to maintain this product's benefit:risk balance. The elements proposed for this REMS are: prescriber certification, pharmacy certification, and documentation of safe use condition (i.e., *Natpara REMS Patient-Prescriber Acknowledgement Form*).

At the time this review was completed, the Natpara REMS document was still undergoing internal FDA review.

DRISK recommends DMEP sends the Applicant all comments included in section 7 of this review, including REMS appended materials.

## 7 COMMENTS FOR THE APPLICANT

1. FDA acknowledges receiving (via email) on November 6, 2014 your draft proposal for Natpara REMS. The REMS proposed by NPS includes the key elements FDA considers necessary for the Natpara REMS (i.e., prescriber certification, pharmacy certification, and documentation of safe use condition); however, the proposed REMS requires additional modifications. The REMS document is undergoing internal FDA evaluation. Once the review process is completed, FDA will send NPS the revised version. The Natpara REMS Program must include prescriber certification, pharmacy certification and

documentation of safe use condition. The following comments will assist you in the development of a REMS for Natpara.

2. REMS message maps for prescribers, pharmacy representatives, and patients – The REMS message maps contain the key risk messages to be addressed by the Natpara REMS. The messages included in these maps must be consistent with the product label (not necessarily verbatim) and will be used to guide the development of all REMS-related documents, including REMS assessment survey questions. A copy of the REMS message maps should be included in the Natpara REMS Supporting Document. See appendix 1 for examples of REMS message maps.
3. *Natpara REMS Letter for Prescribers* – A REMS Letter for Prescribers is a shorter, REMS message-focused communication [REDACTED] (b) (4) [REDACTED]. See appendix 2 which includes two examples of the *Natpara REMS Letter for Prescribers*; one is intended for email use and the other version is intended for printing, depending on NPS' decision to use email or regular mail (print format) to distribute REMS Letters along with other REMS materials among prescribers who attempt to prescribe Natpara and are not yet certified, or inquire about how to become certified.
4. Prescriber certification – Prescriber certification consists of training and enrollment. To become certified in the Natpara REMS Program, prescribers must:
  - review the Prescribing Information for Natpara, and *Natpara REMS Program: An Introduction* sheet mentioned above.
  - complete the *Natpara REMS Training Module for Prescribers*, and
  - complete and sign the *Natpara REMS Prescriber Enrollment Form* and submit it to the Natpara REMS Program Coordinating Center.NPS will establish the Natpara REMS Program Coordinating Center and will send prescribers confirmation of certification.
  - a. *Natpara REMS Training Module for Prescribers* – An example of the training module part of the prescriber certification process is included in appendix 3.
  - b. *Natpara REMS Prescriber Enrollment Form* – An example of the Prescriber Enrollment Form part of the prescriber certification process is included in appendix 4.
  - c. *Natpara REMS Program: An Introduction* – This is a REMS Program introduction sheet which summarizes all the key components of the Natpara REMS Program. See appendix 5.
5. Pharmacy certification – Pharmacy certification entails the selection of a Pharmacy Representative who will receive training and enroll the pharmacy in the Natpara REMS Program. The Pharmacy Representative must:
  - review the Prescribing Information for Natpara, and *Natpara REMS Program: An Introduction* sheet

- complete the *Natpara REMS Training Module for Pharmacy Representatives*, and
- complete and sign the *Natpara REMS Pharmacy Enrollment Form* and submit it to the Natpara REMS Program Coordinating Center.

NPS will send confirmation of pharmacy certification to the Pharmacy Representative. Prior to dispensing Natpara, the pharmacy will: (1) verify the prescriber is certified in the Natpara REMS Program by contacting the Natpara REMS Program Coordinating Center prior to dispensing Natpara and (2) verify that a *Natpara REMS Patient-Prescriber Acknowledgement Form* is on record for the corresponding patient and prescriber by contacting the Natpara REMS Program Coordinating Center.

- a. *Natpara REMS Training Module for Pharmacy Representatives* – An example of the training module part of the pharmacy certification process is included in appendix 6.
  - b. *Natpara REMS Pharmacy Enrollment Form* – An example of the Natpara Pharmacy Enrollment Form part of the prescriber certification process is included in appendix 7.
  - c. *Natpara REMS Program: An Introduction* – see comment above.
6. *Natpara Patient Brochure* – Prescribers will use the *Natpara Patient Brochure* as a counseling tool to assist in the benefit:risk discussion that must take place prior to initiation of treatment with Natpara. See an example of the patient brochure in appendix 8.
  7. *Natpara REMS Prescriber-Patient Acknowledgement Form* – Prescriber and pharmacy certification alone does not guarantee that each patient will be informed about the benefits and potential risk for osteosarcoma associated to Natpara. The patients and prescriber will complete and sign a *Natpara REMS Patient-Prescriber Acknowledgement Form* documenting the discussion of the benefits and risks associated to Natpara occurred prior to the initiation of therapy. Once completed, the *Natpara REMS Patient-Prescriber Acknowledgement Form* is faxed or sent electronically via email to the Natpara REMS Program Coordinating Center. See appendix 9.

The *Natpara REMS Prescriber-Patient Acknowledgement Form* and the *Natpara Patient Brochure* should be included in as one.PDF file. The intent is that the prescriber can print both documents at the same time and provide the patient with the Patient Brochure when the patient signs the Patient-Prescriber Acknowledgement Form.

8. *Natpara REMS Website* – The REMS website should be available via a prominent, REMS-specific link in the Natpara commercial website for the duration of the REMS. This link should direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. The separate REMS website should contain background information on the REMS along with the REMS appended materials. The Natpara REMS website will include the option to print versions of the Natpara REMS materials. The content of the website should be easily viewed in a handheld device. Ensure the REMS website ([www.NATPARAREMS.com](http://www.NATPARAREMS.com)) is independent of links to the

promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the REMS website back to the commercial website (www.NATPARA.com). The REMS website should also be accessible directly through a search engine. See appendix 10 for an example of a REMS landing page.

9. General comments

- a. Education or communication provided as part of a REMS should emphasize the safety messages important for the safe use of the product.
- b. Product marketing materials generally are not appropriate to educate about product risks.
- c. Please submit all planned materials (e.g., proposed communications, education materials, and REMS website) identified within the plan that will be necessary to implement your proposal.
- d. When feasible, we recommend pre-testing all REMS materials.
- e. Submit all revisions to the REMS documents in track changes and clean MS Word versions.

When addressing comments from FDA reviewers, in addition to tracking changes in the REMS documents, please provide a summary table in MS Word listing all revisions proposed by NPS to REMS documents and rationale for the change. (See example provided below).

<b>Natpara REMS: Summary of Changes</b>	
<b>NPS revisions/comments</b> mm/dd/yyyy	<b>FDA revisions/comments</b> mm/dd/yyyy
<b>Global/General comments</b>	
<i>Comment</i>	
<i>Comment</i>	
<b>REMS Document</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara REMS Letter for Prescribers</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara REMS Program: An Introduction</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara REMS Training Module for Prescribers</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara REMS Training Module for Pharmacy Representatives</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara REMS Prescriber Enrollment Form</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	

<b>Natpara REMS Pharmacy Enrollment Form</b>	
<i>Line #X-Y: Comment</i>	
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<b>Natpara Patient Brochure</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara REMS Patient-Prescriber Acknowledgement Form</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara REMS Website (landing page)</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	

Appended Materials

Appendix 1 – Natpara REMS Message Maps

Appendix 2 – Natpara REMS Letter for Prescribers

Appendix 3 – Natpara REMS Training Module for Prescribers

Appendix 4 – Natpara REMS Prescriber Enrollment Form

Appendix 5 – Natpara REMS Program: An Introduction

Appendix 6 – Natpara REMS Training Module for Pharmacy Representatives

Appendix 7 – Natpara REMS Pharmacy Enrollment Form

Appendix 8 – Natpara Patient Brochure

Appendix 9 – Natpara REMS Patient-Prescriber Acknowledgement Form

Appendix 10 – Natpara REMS Website

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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: June 19, 2014

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer  
Division of Risk Management (DRISK)

Team Leader: Doris Auth, Pharm D, Team Leader, DRISK

Division Director: Claudia Manzo, Pharm.D, Director DRISK

Subject: Evaluation of need for a REMS – deferral of comments

Drug Name(s): Natpara<sup>®</sup>, recombinant Human Parathyroid Hormone [rhPTH(1-84)] for injection

Therapeutic Class: Parathyroid hormone

Dosage and Route: 25 mcg, 50 mcg, 75 mcg, and 100 mcg; subcutaneous injection

Application Type/Number: BLA 125511

Submission Number: Sequence No.0000 and 0011

Applicant/sponsor: NPS Pharmaceuticals

OSE RCM #: 2013-2500 and 2013-2496

**\*\*\* This document contains proprietary and confidential information \*\*\*  
that should not be released to the public.**

## 1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of whether a Risk Evaluation and Mitigation Strategy (REMS) is necessary for Recombinant Human Parathyroid Hormone [rhPTH(1-84)] for injection (BLA 125511). On January 19, 2014, FDA granted approval to the proposed proprietary name, Natpara. NPS Pharmaceuticals is seeking approval for Natpara as replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism.

The active pharmaceutical ingredient in Natpara (rhPTH(1-84)), is identical to the human amino acid protein and has been developed for the treatment of hypoparathyroidism and for the treatment of osteoporosis. At the time this review was completed, rhPTH(1-84) has not been approved for the indication of treatment of hypoparathyroidism in any jurisdiction but was granted marketing authorization (2006) in the European Union, Iceland, Liechtenstein, and Norway for the "treatment of osteoporosis in postmenopausal women at high risk of fractures".

NPS Pharmaceuticals did not submit a Risk Evaluation and Mitigation Strategy (REMS) but did include a risk management plan (RMP) with this application.

### 1.1 BACKGROUND

*Parathyroid Hormone (PTH)*<sup>1</sup> – Parathyroid hormone is an 84-amino acid protein secreted by the parathyroid glands. Parathyroid hormone has many functions including the regulation of bone metabolism and serum levels of calcium and phosphate. Hypoparathyroidism results in low level of serum calcium (hypocalcemia) and a high serum level of phosphate, increased urinary calcium excretion and decreased urinary phosphate excretion. Hypocalcemia may present with the following signs and symptoms: numbness, paresthesia, twitching, tetany, seizures, cardiac arrhythmias, cardiomyopathy and laryngeal spasm.

Causes of hypoparathyroidism include permanent damage to or removal of parathyroid glands or their blood supply during neck surgery, autoimmune conditions, congenital absence of the parathyroid glands (DiGeorge syndrome), genetic mutations, iron overload syndromes, and radiation damage. The current treatment of hypoparathyroidism consists of supplemental oral calcium and vitamin D; however, supplementation alone is palliative because it does not correct all the metabolic derangements caused by the absence of PTH. In addition, finding the right doses of these two supplements to avoid under or overtreatment is often challenging. Potential long-term complications of calcium and vitamin D supplementation include soft tissue calcifications (kidney stones, basal ganglia) and end-organ damage (kidney, eye, and central nervous system).

*Natpara*<sup>1</sup> – The active pharmaceutical ingredient, rhPTH(1-84), is identical to the full-length human 84-amino acid protein. rhPTH(1-84) is manufactured using a strain of *Escherichia coli* modified by recombinant deoxyribonucleic acid (rDNA) technology. Natpara for injection is supplied as a multiple dose, dual-chamber cartridge which is available in 4 dosage strengths (25, 50, 75, or 100 µg). The Natpara<sup>®</sup> Mixing Device and Natpara Q-Cliq<sup>™</sup> were developed specifically for rhPTH(1-84).

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<sup>1</sup> Clinical Overview, submitted to FDA on October 23, 2013

## 1.2 REGULATORY HISTORY

- **January 31, 1995:** Investigational New Drug (b)(4) for the investigation of rhPTH(1-84) in osteoporosis was originally submitted to FDA.
- **May 10, 2005:** NPS submitted a New Drug Application (NDA (b)(4)) for rhPTH(1-84) under the proprietary name Preos® for the therapeutic indication, “Treatment of postmenopausal women with osteoporosis”.
- **March 9, 2006:** NDA (b)(4) received an approvable letter with key issues relating to safety associated with hypercalcemia and reliability of the delivery device used in the clinical trials. FDA required an additional Phase 3 study to obtain final approval for the product in the osteoporosis indication; (b)(4)
- **March 24, 2011:** Sponsor withdrew NDA (b)(4) without prejudice.
- **August 2007:** FDA granted Orphan Drug Designation for NPSP558 (rhPTH(1-84)) for hypoparathyroidism.
- **September 19, 2008:** IND 076514 (rhPTH(1-84)) was submitted to conduct the Phase 3 pivotal study, CL1-11-040, for the hypoparathyroidism indication.
- **December 23, 2011:** FDA confirmed that rhPTH(1-84) should be designated as a biologic
- **February 5, 2013:** Type C meeting held to discuss the draft protocol (PAR-C12-002) for the second human factors validation study pertaining to the training and use of the Natpara Q-Cliq and Mixing Device.
- **October 23, 2013:** NDA 125511(rhPTH(1-84)) was received by FDA.
- **January 19, 2014:** FDA granted approval to the proposed proprietary name, Natpara.
- **July 24, 2014:** Scheduled Advisory Committee meeting

## 2 MATERIALS REVIEWED

### 2.1 INFORMATION SOURCES

- Clinical Overview, submitted to FDA on October 23, 2013.
- US Risk Management Plan, dated October 3, 2013, received by FDA October 23, 2013.
- NPS Pharmaceuticals response to FDA’s Information Request, received by FDA February 6, 2014.
- Natpara, March 19, 2014 mid-cycle meeting briefing slides.

## 3 CLINICAL DEVELOPMENT PROGRAM

The clinical development program for rhPTH(1-84) includes 12 clinical pharmacology studies, 5 efficacy and safety studies in hypoparathyroidism (4 sponsored by NPS and the Bilezikian IIT, Table 1), and a supporting development program consisting of 7 studies in osteoporosis.

The pivotal study, Study CL1-11-040, is a randomized, double-blind, and placebo-controlled study. The primary endpoint in this study was a composite consisting of 3 components: (1) >50% reduction in the baseline dose of active vitamin D at Week 24, (2) >50% reduction in the baseline dose of oral

calcium at Week 24, and (3) maintenance at Week 24 of a stable albumin-corrected total serum calcium level ( $\geq 7.5$  mg/dL) as compared with the optimized level achieved on currently available therapy (calcium and active vitamin D) at baseline.

### 3.1 KEY EFFICACY AND SAFETY FINDINGS

Key efficacy and safety findings are the subject of discussion at the upcoming advisory committee meeting July 24, 2014.

The Applicant reports that in the pivotal study, the percentage of responders in the Intent-to-Treat (ITT) population was higher in the rhPTH(1-84) group (53.3%) compared with the placebo group (2.3%). The difference between groups was clinically and statistically significant ( $p < 0.001$ ). Key safety concerns identified by the Applicant include hypercalcemia during initiation of Natpara therapy and hypocalcemia associated with abrupt withdrawal of Natpara therapy.

**Table 1. Efficacy and Safety Studies in Hypoparathyroidism**

Study Number	Study Objectives	Study Design and Type of Control	rhPTH(1-84) Dose <sup>a</sup>	Number of Subjects	Duration of Treatment
<b>NPS Sponsored Efficacy and Safety Studies in Hypoparathyroidism</b>					
CL1-11-040 (REPLACE)	Efficacy and Safety	Randomized, double-blind, placebo-controlled	50, 75, and 100 µg (flexible doses) or placebo	rhPTH(1-84), 90; Placebo, 44	24 weeks
PAR-C10-007 (RELAY)	Efficacy and Tolerability	Randomized, dose-blinded	25 or 50 µg (fixed doses)	25 µg, 23; 50 µg, 24	8 weeks
PAR-C10-008 (RACE)	Safety and Tolerability	Open-label	25, 50, 75, and 100 µg (flexible doses)	53	52 weeks + extension <b>ONGOING</b>
PAR-C10-009 (REPEAT)	Safety and Tolerability	Open-label	50, 75, and 100 µg (flexible doses)	24	24 weeks
<b>Bilezikian IIT in Hypoparathyroidism</b>					
Bilezikian IIT	Safety and Efficacy	Open-label study, prospective	25, 50, 75, and 100 µg (flexible doses)	79	6 month pilot + 2-year study with multiple 1-year extensions <b>ONGOING</b>

IIT = investigator-initiated trials

<sup>a</sup> All doses of rhPTH(1-84) in the NPS-sponsored studies were daily SC injections in the thighs. Dosing in the Bilezikian IIT was either daily or less than daily.

Source: Adapted from Module 2.7.6; PAR-C10-007 CSR

Source: Clinical Overview rhPTH(1-84), page 21.

## 4 APPLICANT'S PROPOSED RISK MANAGEMENT PLAN

NPS Pharmaceuticals did not propose a REMS but included a RMP in this submission. The submitted RMP provides a high level description of NPS Pharmaceuticals' commercial support plan which includes the post-approval implementation of the mitigation strategy tested in the Human Factor Study (included as part of this submission). The proposed plan includes:

- distribution of Natpara via a restricted specialty pharmacy network;
- healthcare professional and patient training before the product is shipped to the patient;
- healthcare provider and patient support provided by NPS Advantage (NPS support program for patients); and

- a requirement for completion of a referral form to document the patient and physician office staff have been properly trained on the use of Natpara and the delivery device.

FDA sent an information request (IR) to the Applicant on January 6, 2014 requesting NPS Pharmaceuticals submitted a fully developed risk management plan proposal including all planned materials necessary to implement the proposed program (e.g., proposed communication and education materials and forms) and a program process flow chart including but not limited to healthcare professionals, patients, and specialty pharmacy staff training approach and program built-in safeguards (e.g., specialty pharmacy role in product distribution, role of NPS Advantage). In addition, FDA requested NPS Pharmaceuticals provided its rationale for why a REMS is not required for this product.

A response to FDA's IR was received on February 6, 2014 (amendment 1255511.07, Sequence Number 0006). The Applicant's response to FDA's IR provided sufficient information to clarify the intent of the proposal and addressed FDA's preliminary questions about the proposed RMP.

Based on this information, FDA informed NPS Pharmaceuticals that, at the time, the Office of New Drugs and the Office of Surveillance and Epidemiology had insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the Natpara outweigh the risks of medication error, hypocalcemia, hypercalcemia, or any other risk to be identified during the review process and, if it is necessary, what the required elements will be. In addition, FDA reminded the Applicant that their proposed RMP will not be approved as a REMS unless and until the FDA determined that it is required to ensure that the benefits of the drug outweigh the risks and that it meets the FDAAA criteria.

## **5 CONCLUSIONS AND RECOMMENDATIONS**

FDA has not yet completed Natpara's benefit-risk assessment. Therefore, DRISK defers comments on the management of the risks associated with Natpara.

Please contact DRISK if you have any questions.

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