CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125511Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Jean-Marc Guettier, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	125,511
Applicant Name	NPS Pharmaceuticals
Date of Submission	October 24, 2013
PDUFA Goal Date	January 24, 2015
Proprietary Name / Established (USAN) Name	NATPARA/Parathyroid hormone
Dosage Forms / Strengths	Powder for injection / 25, 50, 75, 100 mcg to be administered subcutaneously each day
Proposed Indication(s)	1. *"Natpara (rhPTH[1-84]) for injection is a replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism"*
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Naomi Lowy, MD
Statistical Review	Jennifer Clark, PhD
Pharmacology Toxicology Review	Robert Maher, PhD
CMC Review/OBP Review	Muthukumar Ramaswamy PhD, Joseph Leginus PhD
Clinical Pharmacology Review	Manoj Khurana PhD
DSI	Cynthia Kleppinger, MD
CDTL Review	Dragos Roman, PhD

OND=Office of New Drugs
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

1. Introduction

On October 24, 2013 NPS submitted a Biologics License Application (BLA) for Natpara under section 351 of the Public Health and Service Act. The applicant is seeking to indicate Natpara *as a replacement for endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism*. Natpara is a parathyroid hormone whose amino acid sequence is the same as endogenous parathyroid hormone. Natpara is supplied as a dual-chamber glass cartridge containing a sterile lyophilized powder and a sterile diluent in four dosage strengths 25, 50, 75 and 100 mcg for reconstitution. The reconstituted drug product is delivered by daily subcutaneous injection into the thigh using a dedicated pen device.

2. Background

Hypoparathyroidism is a clinical syndrome that results from parathyroid gland hypo-function and is characterized by low or normal circulating parathyroid hormone (PTH) levels in the setting of hypocalcemia. Hypoparathyroidism is most often caused by inadvertent removal of the parathyroid glands during thyroidectomy or as a result of autoimmune or congenital diseases. Hypoparathyroidism is a rare disease estimated to affect approximately 60,000 individuals in the United States.

Parathyroid hormone plays a key role in calcium homeostasis. Parathyroid hormone (PTH) secretion from the parathyroid glands is controlled by ambient calcium concentration. Low calcium levels stimulate the parathyroid glands to increase PTH secretion. PTH acts distally to augment; renal tubular calcium reabsorption, intestinal calcium absorption (i.e., by converting 25 hydroxyvitamin D to 1,25 dihydroxyvitamin D) and bone turnover which releases calcium from bone. These PTH effects will raise circulating calcium levels until calcium concentration is sufficiently high to feedback on the parathyroid glands and return PTH secretion to baseline levels.

The clinical manifestations of hypoparathyroidism are a direct consequence of parathyroid gland hypo-function. Patients with hypoparathyroidism have symptoms and signs related to acute hypocalcemia[1] and complications attributed to; chronic hypocalcemia (i.e., cardiomyopathy), chronically elevated phosphorus levels (i.e., central nervous system and vascular extracellular calcification), low bone turnover (i.e., increased bone mass and bone fragility) and chronic hypercalciuria (i.e., nephrocalcinosis, nephrolithiasis, and progressive renal impairment).

Treatment with oral calcium supplements and active forms of Vitamin D is the current standard of care for hypoparathyroidism. The goal of therapy is to correct low calcium levels sufficiently to; prevent hypocalcemia, minimize hypercalciuria, and minimize the risk of

[1] numbness, paresthesia, musculoskeletal irritability [i.e., twitching, tetany, cramps), seizures, cardiac arrhythmias (due to QT prolonging effect), and laryngeal spasms

extracellular calcification. There are needs not currently addressed by the available standard of care treatment. First, adjustment of serum calcium using supplemental calcium and vitamin D is imprecise. Under-treatment may result in acute or chronic hypocalcemia. Overtreatment can result in acute or chronic hypercalcemia and hypercalciuria. In addition, patients may be inconvenienced by the need to ingest oral calcium supplements multiple times daily to maintain normocalcemia and may not be able to tolerate large doses of calcium due to side effects of this therapy (e.g., constipation). Finally, current therapies do not address the underlying renal calcium handling or bone turnover abnormalities that result from abnormal parathyroid gland function.

Regulatory History

NPS pharmaceuticals developed the same drug product, parathyroid hormone, under the trade name Preos for the treatment of osteoporosis in post-menopausal women at high risk of bone fracture. A new drug application was submitted for this indication in May 2005. The Agency did not authorize marketing of Preos, at that time, because of safety concerns identified in the application. As a path forward, the applicant was asked to address the observation of a significant risk of hypercalcemia associated with the proposed daily dosing regimen (b) (4) and to address safety issues related to the reliability and use of the proposed to-be commercialized device. The Applicant withdrew the NDA for this indication in 2011.

The Investigational New Drug (IND) Application for the hypoparathyroidism indication was opened in 2006 and the product received Orphan Drug Designation in 2007. Dr. Roman has summarized, in Section 2 of this CDTL memorandum, the regulatory interactions for the hypoparathyroidism indication. Refer to this memorandum for details.

3. CMC/Device

I concur with the conclusions reached by the CMC/Device reviewers that there are no outstanding CMC/Device issues that preclude approval. Natpara is supplied as a dual-chamber glass cartridge containing a sterile lyophilized powder and a sterile diluent, within a plastic cartridge holder. The stability studies support an expiration date of 24 months when the un-reconstituted product is stored between 2 and 8 degrees Celsius. Once reconstituted, the suspension can be used for up to 14 days provided the product is stored between 2 and 8 degrees Celsius. The medication cartridge is designed for use with a reusable mixing device for product reconstitution and a dedicated reusable pen device (Q-Cliq pen) for product delivery into the subcutaneous tissue.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by Dr. Maher, the nonclinical pharmacology/ toxicology reviewer, that there are no outstanding nonclinical pharmacology/toxicology issues that

preclude approval. The main acute and chronic toxicology findings were osteosarcoma, risks related to an exaggerated pharmacodynamic response which manifested as tissue mineralization (cardiac, renal) secondary to chronic hypercalcemia and as decreased blood cells from an exaggerated bone anabolic effect and developmental effects in animal reproduction studies.

Dr. Roman in his CDTL memorandum has summarized the findings from the rat carcinogenicity study with parathyroid hormone (1-84), the active ingredient in Natpara. In this study both male and female rats exposed to parathyroid hormone (1-84) were observed to have an increased incidence of osteosarcoma. The occurrence of osteosarcoma was observed to be dependent on parathyroid hormone dose and treatment duration. The response between dose and incidence was robust (33% incidence in the highest dose group versus 0-1.6% in controls). The effect was observed at parathyroid hormone exposure levels ranging from 3 to 71 times the exposure levels for humans receiving 100 mcg daily. When these findings were presented at the Executive Carcinogenicity Assessment Committee, members did not find that the safety margin provided sufficient reassurance to exclude human relevance. The nonclinical pharmacology/toxicology reviewers have concluded that the risk of osteosarcoma for PTH 1-84 (i.e., the active ingredient in Natpara) is similar to that of PTH 1-34 (i.e., the active ingredient in Forteo).

The findings of osteosarcoma in carcinogenicity studies of PTH and PTH analog products was considered for the application of another PTH related peptide [i.e., PTH (1-34)] which is approved and indicated for the treatment of osteoporosis in various settings [refer to Forteo full prescribing information]. Biologic plausibility is suggested by the fact that the cellular origin of osteosarcoma, the osteoblast/osteoblast progenitor cell, is also the cellular target for PTH in bone and by the robust dose-risk relationship observed in carcinogenicity studies. Estimating the relevance to humans is complicated by the fact that bone physiology in rats differs from that of humans, by the fact that rats were exposed to high doses of drug from a young age and for a large fraction of their lifespan (tumors appeared after 50-75% of lifespan) and by the fact that, in humans, osteosarcoma is rare (2-4 cases per million person-years) and that clinical development programs, with exposure of a few thousand patients over 1-2 years, are grossly underpowered to detect all but very large risk increases.

For example, assuming the incidence of osteosarcoma in the general population is 1 case per 333,000 person-years and applying the rule of three: it would take 999,000 patients observed for a year to capture at least one event in a clinical program. If the risk is increased 10-fold, 100-fold, 1000-fold it would take 99,900, 9990, and 999 patient exposed-for a year respectively to detect at least one event. In the Natpara clinical program for example (including the osteoporosis development program) ~ 2000 adult patients were observed for ~ 1-year and the fact that no cases were observed can only reliably exclude a 1000-fold risk increase.

Applicants point to hyperparathyroidism, a common disease associated with mild chronic increases in PTH, to argue against the human relevance of the rat findings. Although

hyperparathyroidism does not appear to be associated with an increased risk of osteosarcoma, it is known that intermittent pharmacologic PTH dosing (e.g., anabolic effect) produces markedly different effects on bone metabolism than tonic/chronic PTH exposure (e.g., catabolic effect). These observations have called into question the relevance of the hyperparathyroid experience with regard to informing the risk of osteosarcoma associated with exogenously administered PTH products.

To mitigate the risk, Forteo was approved with; a Black Box Warning communicating the risk of osterosarcoma and an indication limited to older individuals with mature skeletons who had failed or could not tolerate available therapies. Recommended duration of use for Forteo has been limited to 2-years.

Two required studies to further assess the clinical risk of osteosarcoma associated with Forteo use are ongoing. One is a surveillance study whose objective is to capture 1/3 of the incident cases of osteosarcoma in the US and assess exposure history to Forteo[2]. This study will be completed in 2019. The second study is a voluntary registry of users of Forteo. In this study, data from registered volunteers are linked to participating cancer registries to ascertain new cases of osteosarcoma in Forteo-exposed patients. The final report for that study is expected in 2022. Interim results from these studies have not altered the risk benefit of Forteo materially to warrant a label change. The Agency has also been monitoring the FDA Adverse Event Reporting System (FAERS) for reports of osteosarcoma associated with Forteo use. Nine cases were identified in FAERS as of September 2014. The case descriptions contained insufficient information to firmly establish a causal relationship between Forteo exposure and osteosarcoma occurrence. Finally, the experience with Forteo and its role in informing the osteosarcoma risk for this application is limited due to the restriction that is placed on Forteo duration of use and on the fact that the long latency predicted from rat studies (equivalent to ~40 human years of exposure to first detect) has not yet elapsed.

In sum, the experience with Forteo has not, to date, provided information to allay or increase concerns with regard to osteosarcoma risk as it pertains to PTH and PTH analog products.

The topic of osteosarcoma risk was discussed at the September 12th 2014 advisory committee for Natpara and the issue was summarized in the minutes as follows:

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

[2] Andrews E, et al. The US Postmarketing Surveillance Study of Adult Osteosarcoma and Teriparatide: Study Design and Findings from the First 7 Years. JBMR. 2012: 27, 2429-2437.

Several issues pertinent to the hypoparathyroidism indication and discussed at the advisosry committee meeting are unique to this indication and are worth highlighting. First, the use of Natpara in patients with hypoparathyroidism will be life-long and not restricted in duration. Second, some committee members felt that populations at increased risk of osteosarcoma (e.g., pediatric patients with growing bones) could benefit from Natpara in spite of the risk and that careful consideration of benefits and risks should be based on circumstances of the individual case. Doctor McBryde and other pediatricians on EMDAC pointed to potential unmet needs in the pediatric population and recommended this therapy not be restricted solely to adult patients. In light of the potential osteosarcoma risk, there was general agreement that use of Natpara should be limited to those failing the standard of care, that labeling should carefully describe the risk of osteosarcoma, and that measures beyond labeling to mitigate risk were needed.

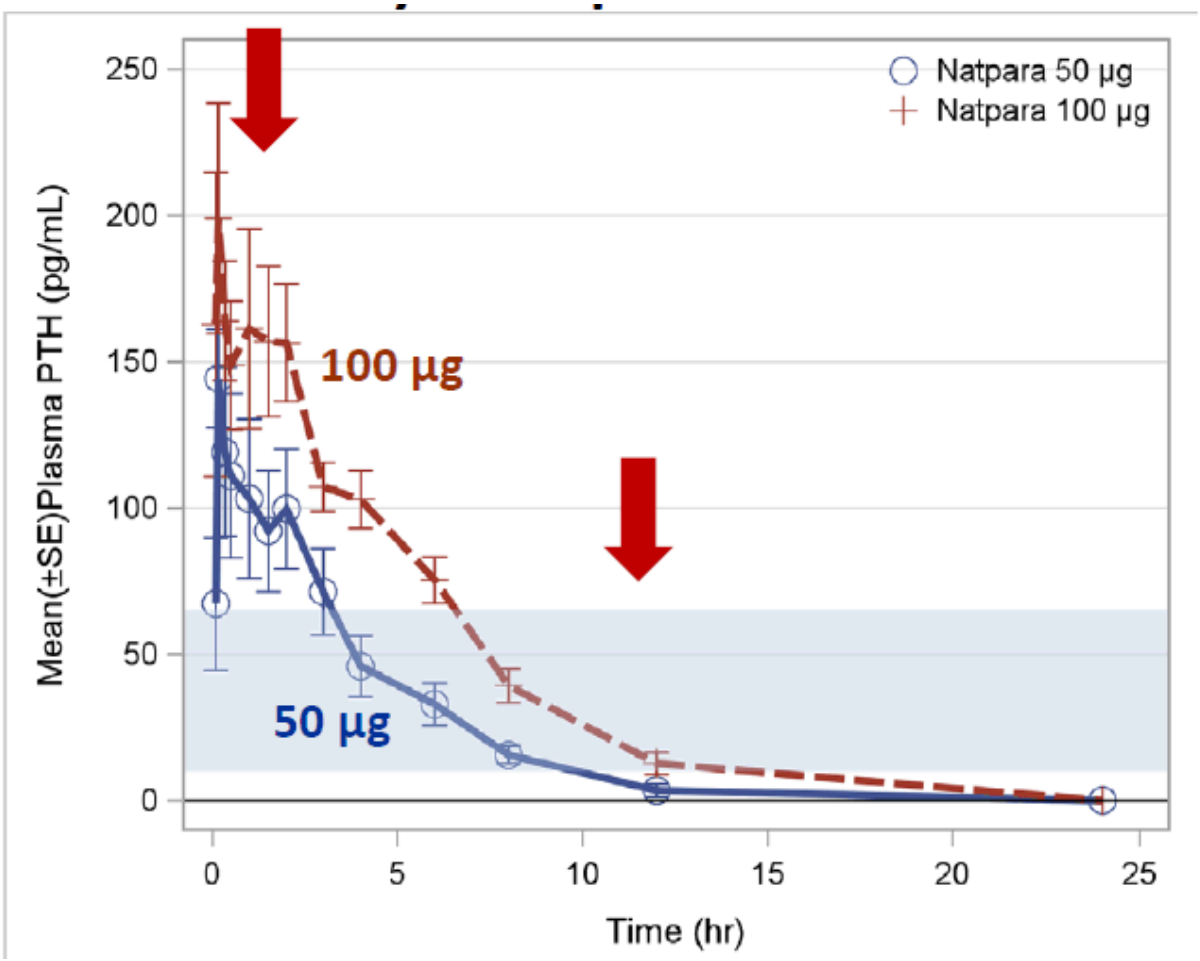
The proposed Risk Evaluation and Mitigation Strategy (REMS) for Natpara was discussed at the REMS oversight committee on October 8th 2014. Dr. Pippins in her memorandum dated January 12th 2015 has summarized the rationale for requiring a REMS with elements to assure safe use (ETASU) and the reader is referred to this memorandum for details. To ensure the benefits of NATPARA outweigh the risks for the hypoparathyroidism indication the REMS will include: elements to ensure safe use, including prescriber certification, pharmacy certification, documentation of a safe use condition (i.e., Patient-Prescriber Acknowledgment Form informing patients of the potential risk of osteosarcoma), an implementation system, and a timetable for submission of assessments of the REMS. As stated by Dr. Pippins, "*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*".

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by Drs. Khurana and Zadezensky, the clinical pharmacology/ biopharmaceutics reviewers, that there are no outstanding clinical pharmacology issues that preclude approval. Key aspects of their review are summarized below.

Single dose administration PK studies in hypoparathyroid patients revealed dose-proportionality within the proposed dosing range, a terminal apparent half-life of ~ 3 hours, a maximal drug concentration achieved within 5 to 30 minutes, and a mean maximum serum concentration (C_{max}) at the 100 mcg dose of ~200 pg/mL. In hypoparathyroidism subjects, a single subcutaneous injection of Natpara results in a dose-dependent increase in serum calcium levels which peak between 10 and 12 hours following the injection and do not return to baseline by 24 hours. These data are illustrated in figures on pages 12 and 13 of Dr. Roman's memorandum. The single dose PK figure (copied below) includes the physiologic

PTH range (blue-shade) and shows that serum PTH following a single 100 mcg subcutaneous dose is within the physiologic normal range for only 7.5 hours of the day. It is above the physiologic range in the first ~7.5 hours post dose and below range from 15 hours post-dose onward. This figure illustrates the fact that Natpara is not physiologic PTH replacement. Dr. Khurana, using modeling techniques, has explored the impact of the selected once daily dosing regimen on 24-hour urinary calcium excretion. The conclusions of these analyses will be discussed briefly in Section 7 of this memorandum. For a full discussion of this issue refer to his memorandum.



6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

Drs. Lowy and Clark have reviewed the efficacy findings in details and Dr. Roman has summarized key findings in his CDTL memorandum. Refer to these reviews for full discussions. The efficacy of Natpara for the treatment of patients with hypoparathyroidism was demonstrated in a single pivotal randomized 24-week controlled trial (REPLACE) which demonstrated that daily injection of Natpara was superior to placebo at maintaining serum calcium levels in the face of reduced doses of calcium supplements and active forms of vitamin D in adult patients with hypoparathyroidism and normal renal function. Maintenance of serum calcium in this condition is directly linked to symptomatic relief and REPLACE establishes the efficacy of the product compared to placebo. REPLACE does not provide substantial evidence to support an advantage of Natpara 100 mcg once daily over currently available therapies with regard to serum calcium maintenance, symptomatic control or improvement in: renal complications, quality of life or bone complications.

REPLACE: Efficacy in Adult Patients with Hypoparathyroidism

The REPLACE trial was a multi-national, multi-center, randomized, double-blind, placebo-controlled trial comparing the efficacy of Natpara to that of a placebo. The primary objective of the trial was to compare the proportion of subjects who met the response criterion at the end of 24 weeks. The response criterion was defined as fulfillment of all of the following three components:

1. a reduction from baseline in the dose of active vitamin D of at least 50%
2. a reduction from baseline in the dose of oral calcium supplementation of at least 50%
3. an albumin-corrected total serum calcium concentration between 7.5 mg/dL and 10.6 mg/dL.

Patients were eligible to participate in the study if they were older than 18 years of age, had hypoparathyroidism for longer than 18 months,[3] were on at least an active form of vitamin D at a dose equivalent to 25 mcg of calcitriol, had normal 25-hydroxyvitamin D and magnesium levels and had a creatinine clearance of > 60 mL/min by the end of the optimization period. The study excluded: patients with hypoparathyroidism caused by calcium sensing receptor (CaSR) mutations, patients with hypoparathyroidism dependent on regular infusion of calcium, patients with hypoparathyroidism with a history of seizures, prevalent diseases known to influence calcium-phosphate metabolism (e.g., paget's, severe and chronic heart liver and renal disease etc.) and use of medications known to influence calcium-phosphate metabolism, and patients with a history of radiotherapy within 5 years preceding the screening visit.

Before randomization, participants entered a 2-16 week run-in phase. In this phase calcium supplement and active vitamin D doses were adjusted to target an albumin-corrected serum

[3] Defined as historical biochemical evidence of hypocalcemia and concomitant serum intact PTH below the lower limit of normal documented on two occasions.

calcium concentration between 8.0 and 9.0 mg/dL and restore 25-hydroxyvitamin D to sufficient levels in those patients with insufficient stores.

At randomization, mean serum calcium was in the normal range at 8.6 mg/dL and participants were receiving a median (interquartile range) daily oral calcium dose of 2000 (1250, 3000) mg and a median daily oral active vitamin D dose equivalent to 75 mcg (50, 100) of calcitriol.

Subjects were randomized 2:1 to daily injections of Natpara 50 mcg per day (N=84) or placebo (N=30)[4]. At randomization, active forms of vitamin D were reduced by 50%. Randomization was followed by a 12-week titration phase and a 12-week dose maintenance phase. During the titration phase the dose of investigational drug was increased by 25 mcg increments every four weeks up to a maximum of 100 mcg. Up-titration was to occur in all patients who could not completely discontinue active vitamin D and reduce oral calcium to supplementation to 500 mg per day or less.

At the end of treatment, 56% of subjects randomized to Natpara were receiving 100 mcg per day, 26% were receiving 75 mcg per day, and 18% were receiving 50 mcg per day. Doses of co-administered active forms of vitamin D and calcium were adjusted (reduced or increased) to maintain albumin-corrected serum calcium within a desired target range throughout the trial in both arms (changes to these medications are discussed below).

Demographics and disease characteristics were mostly balanced at baseline. Overall the study population was comprised of middle age adults, female (~80%), Caucasian (96%) and Asian (~2%). The mean age (range) at baseline was 47 (19-74) years and on average patients had been diagnosed for 15 years prior to randomization. Hypoparathyroidism was caused by post-surgical complications in 71% of cases, idiopathic hypoparathyroidism in 25%, Di George Syndrome in 3%, and auto-immune hypoparathyroidism in 1%. Patients with hypoparathyroidism due to calcium-sensing receptor mutations were excluded from the trial. The mean eGFR at baseline was 97.4 mL/min/1.73 m2 and 45%, 10% and 0% had mild, moderate and severe renal impairment, respectively, at baseline.

More patients randomized to placebo discontinued before Week 24 (i.e., 7% versus 16% for Natpara versus placebo). Subjects on Natpara were more likely to drop out due to an adverse event and subjects randomized to placebo more likely to drop out as a result of subject or investigator decision.

The primary analysis was performed on all randomized patients, used an LOCF strategy to handle data missing at Week 24 and compared the proportion of responders at end of treatment between the two treatment arms.

[4] Ten additional patients randomized were excluded from the efficacy analyses due to major protocol and good clinical practices violations discovered during a routine inspection (refer to Dr. Cynthia Kleppinger's review for details). Inclusion of these patients would not materially change overall efficacy conclusions (see Table 6 in Dr. Clark's review).

The proportion of responders based on the primary analysis and using a conservative method to handle missing information are shown in the table below. Significantly more subjects randomized to Natpara met the response criterion compared to subject randomized to placebo and the conclusion of superiority was not affected by even the most conservative assumptions regarding missing data.

Table 1: Proportion of Patients Achieving Normalization at Week 24 in Main Analysis and One Sensitivity Analysis (Source: Adapted from Table 5 in Dr. Clark's review)

	Natpara (N=84)		***Placebo (N=40)***			
	%	***(Exact 95% CI)***	***%***	***(Exact 95 % CI)***	***Treatment Difference (95% CI)***	***p-value***
LOCF	*54.8*	*(43.5, 66.7)*	*2.5*	*(0.06, 13.2)*	*52.3 (40.6, 64.0)*	*<0.0001*
Worst Case Analysis[5]	*52.3*	*(41.2, 63.4)*	*22.3*	*(10.8, 38.5)*	*29.9 (13.1, 46.7)*	*0.0019*

The primary endpoint was a three component composite requiring that patients satisfy all three components to meet the response criterion. We examined the proportion of patients satisfying each of the three components individually at end of trial. More subjects on Natpara reduced their doses of: active vitamin D by 50% (87% versus 45%) and calcium supplement by 50% (70% versus 8%) compared to subjects on placebo. The median dose of calcium supplement at end of trial was 2000 mg and 750 mg in the placebo and Natpara group respectively. The median dose of active vitamin D at end of trial was 75 mcg and 0 mcg in the placebo and Natpara group respectively. The proportion of individuals with a serum calcium between 7.5 and 10.6 mg/dL (i.e., from slightly below to the upper limit of the normal reference range) was similar between the two groups (88% versus 87%).

At the end of the REPLACE trial subjects on Natpara reduced their oral calcium dose by an average of 52% while patients randomized to placebo increased their dose by 2% ($p<0.001$). Forty-two percent and 3% of patients randomized to Natpara and placebo respectively had discontinued active vitamin D altogether and reduced calcium supplementation dose to ≤500 mg daily by trial end.

Mean serum calcium levels and mean 24-hour urinary calcium excretion were higher for patients randomized to Natpara than for patients randomized to placebo for most of the trial duration. In fact for all but the last visit, subjects randomized to Natpara had a mean urinary calcium value above the desired therapeutic range (i.e., 300 mg/24; shown as a dashed red line in figure 2). This is illustrated in the following two figures.

[5] Assumes missing in Natpara were non-responders and missing in Placebo were responders.

Figure 1: Mean (SE) serum calcium by visit (mg/dL) [Source: FDA Advisory Committee presentation Slide#66]

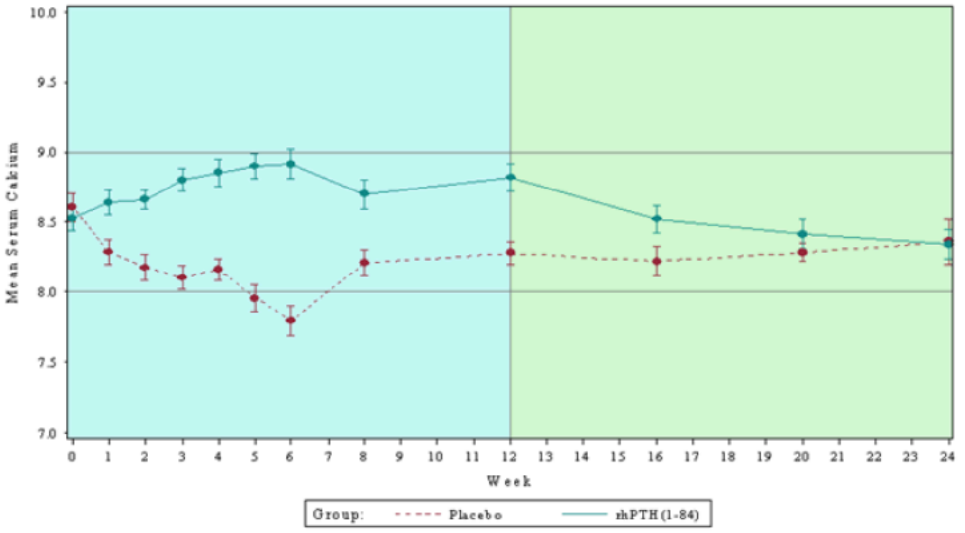
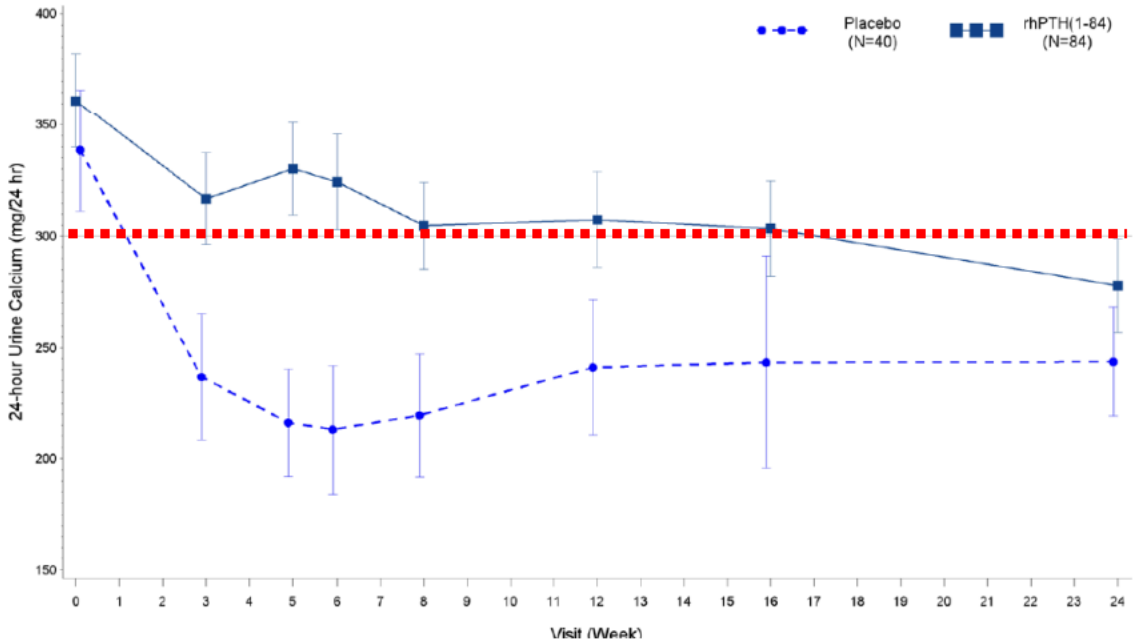


Figure 2: Mean 24-hour Urinary Calcium Excretion (mg/24hrs) [Source: FDA Advisory Committee presentation Slide#78]



Although a decrease in urinary calcium excretion would be expected with physiologic PTH replacement, a salutary effect on urinary calcium excretion was not demonstrated with once daily pharmacologic PTH dosing in REPLACE. This was true even at Week-24 when mean serum calcium levels were similar between groups [Median (IQR) 24-hour calcium excretion: 231 (168-351) versus 232 (139-342) mg/24 hours for Natpara versus Placebo].

The fact that all subjects had a decrease in baseline levels of hypercalciuria and that subjects randomized to vitamin D dose reduction and placebo were more likely to be within desired

urinary calcium excretion goals than subjects randomized to Natpara suggests patients were overtreated with vitamin D and calcium supplementation at baseline.

Drs. Dragos and Lowy have discussed findings based on secondary or exploratory endpoints including: serum phosphorus levels, dual x-ray absorptiometry data and bone formation/resorbption marker data in their reviews. I agree with their assessment that these are exploratory and that changes in these endpoints do not provide direct evidence of a therapeutic benefit beyond serum calcium maintenance.

Dr. Khurana, using modeling techniques, has explored the impact of the selected once daily dosing regimen on 24-hour urinary calcium excretion. He concludes that alternative dosing regimens (twice daily dosing, delayed release or pump dosing) could provide greater salutary effects on 24-hour urinary calcium excretion. These modeling data suggest that alternative dosing regimens could improve the overall benefit risk of the drug and fill a need not met by current standard of care therapies. These are interesting observations and the goal of minimizing risks associated with exaggerated pharmacodynamics (i.e., hypercalcemia, hypercalciuria) through optimization of the formulation or dosing regimen will tested in the post-marketing setting.

8. Safety

Drs. Lowy has reviewed the safety findings in detail. Dr. Roman has summarized the findings in his CDTL memorandum. The main safety issues identified in the review included issues related to the finding of osteosarcoma in the rat carcinogenicity studies discussed in Section 2 of this memorandum and adverse reactions related to exaggerated pharmacodynamics effects (hypercalcemia/hypercalciuria), or underdosing/withdrawal (hypocalcemia).

Immunogenicity was reviewed by Dr. Montserrat; she concludes that the immunogenicity assessment submitted is acceptable and that no correlations between immunogenicity and safety or efficacy signals were observed. She caveats her summary by noting that data on which her conclusions are based are limited. Although the rate of immunogenicity appeared to be numerically higher in this population compared to the osteoporosis population she questions whether this is due to the differences inherent to these populations, changes to the container-closure system or changes to the assay. Immunogenicity will be followed in the post-marketing studies.

Although there were five NPS clinical studies in the Natpara hypoparathyroidism program supporting safety analyses[6] the studies did not recruit unique patients. All in all, 121 unique patients[7] with hypoparathyroidism received at least one dose of Natpara in the clinical

[6] [REPLACE (24-weeks), RELAY (8-weeks), RACE (52-week open-label voluntary extension of REPLACE), REPEAT (24-weeks) and CK09-002 (single dose PK)]

[7] Excludes data derived from site with major GCP violation which was regarded as unreliable.

program. REPLACE was the largest study, it was also randomized and the only placebo controlled study. This study was viewed as the most informative with regard to defining the common adverse reaction and general safety profile of the drug as other studies were uncontrolled voluntary extensions of parent trials, dose exploration studies, ongoing trials or single dose clinical pharmacology studies. The mean (SD) Natpara exposure duration in REPLACE was 168 (26) days. Forty four patients were exposed to Natpara for two years or more when including all studies and extensions in the program.

No deaths were reported in REPLACE (or any other studies) and rates of serious adverse events were comparable between randomized groups (refer to Table 26 in Dr. Lowy's review). Common adverse reaction profile did not suggest Natpara was better tolerated than placebo added to the standard of care as signs and symptoms of hyper and hypocalcemia were numerically more frequent in subjects receiving Natpara during the trial. This is shown in the following figure included in Section 6 of labeling.

Table 1: Common Adverse Reactions associated with NATPARA use in Subjects with Hypoparathyroidism

Adverse Reaction	Placebo (N=40) %	NATPARA (N=84) %
Paraesthesia	25	31
Hypocalcemia*	23	27
Headache	23	25
Hypercalcemia*	3	19
Nausea	18	18
Hypoaesthesia	10	14
Diarrhea	3	12
Vomiting	0	12
Arthralgia	10	11
Hypercalciuria*	8	11
Pain in extremity	8	10
Upper respiratory tract infection	5	8
Abdominal pain upper	3	7
Sinusitis	5	7
Blood 25-hydroxycholecalciferol decreased	3	6
Hypertension	5	6
Hypoaesthesia facial	3	6
Neck pain	3	6

* Hypocalcemia combines reported events of hypocalcemia and blood calcium decreased' hypercalciuria combines reported events of hypercalciuria and urine calcium increased, and hypercalcemia combines reported events of hypercalcemia and blood calcium increased.

There were more episodes of severe hypercalcemia in patients receiving Natpara with some patients requiring temporary hospitalization to correct the abnormality (refer to page 84 of

Dr. Lowy's review). As stated earlier this is likely the result of exaggerated pharmacodynamics. These episodes were more frequent when doses of co-administered calcium raising drugs were being down-titrated (i.e., immediately after randomization as shown in table 2 of the label). This risk is highlighted in Section 5 of the label and mitigated against with dosing recommendations and emphasis on the importance of adherence to serum calcium monitoring.

Table 2 Proportion of Subjects with Albumin-Corrected Serum Calcium Greater Than Upper Limit of Normal (10.6 mg/dL) During the Treatment Period

	Titration Period (Weeks 0-12)*		Maintenance Period (Weeks 12-24)	
Albumin-corrected serum calcium	Placebo N=40	NATPARA N=84	Placebo N=40	NATPARA N=84
>10.6 to ≤12 mg/dL	0%	30 %	0%	10%
>12 to ≤13 mg/dL	0%	2%	3%	0%

Episodes of severe biochemical hypocalcemia (i.e., measured serum calcium level < 7 mg/dL) were observed more frequently in patients randomized to placebo in the titration phase and in patients randomized to Natpara in the maintenance phase. In the titration phase, subjects randomized to placebo had had a 50% reduction in the dose of one their calcium raising drugs (i.e., active vitamin D) and the finding of increased incidence of hypocalcemia was not surprising. These data are shown in Table 3 of the product label and copied below.

Table 3 Proportion of Subjects with Albumin-Corrected Serum Calcium Below the Lower Limit of Normal (8.4 mg/dL) During the Treatment Period

	Titration Period (Weeks 0-12)		Maintenance Period (Weeks 12-24)	
Albumin-corrected serum calcium	Placebo N=40	NATPARA N=84	Placebo N=40	NATPARA N=84
≥7 to < 8.4 mg/dL	98%	79%	75%	71%
<7 mg/dL	18%	6%	0%	12%

The maintenance phase can be considered a comparison to the standard of care since by that time co-administered calcium raising drug doses had been optimized in both arms. These data are consistent with the adverse reaction profile above and suggest that Natpara 100 mcg once daily does not confer an advantage, and indeed appears to confer a disadvantage, over the standard of care when it comes to calcium control.

The risk of severe hypocalcemia requiring medical attention was increased when Natpara was withdrawn at end of trial. This risk increased in spite of a recommendation to resume pre-trial calcium raising drugs. This is an important issue to highlight to ensure patients in the clinical care setting do not skip doses, inform their care providers that they are on Natpara so that this medication is not interrupted (i.e., such as during hospitalization or surgical procedure etc.). This risk and mitigation strategies are described in Section 5 of the product label.

9. Advisory Committee Meeting

Efficacy and safety issues were discussed at an Advisory Committee on September 12th 2014.

The committee members were asked whether efficacy and safety data in the Natpara development program supported approval of Natpara for the long-term treatment of hypoparathyroidism. The outcome of the vote is shown below.

Yes=8, No=5, Abstain=0

Committee Discussion:

A slight majority of the committee agreed that the overall risk benefit of Natpara administered at the doses and regimen proposed supported approval of Natpara for the longterm treatment of hypoparathyroidism.

Dr. Weinstein (the hypoparathyroid expert on the committee) captured in his comments the ambivalence of most members. Some of his commentary is excerpted below.

"I, in the end, voted yes. I would honestly say I was very much on the fence with this, and perhaps at another time, or another moment, I could have made my vote the other way. I think one could make good arguments one way, for one vote or the other to be honest.

That being said, the main reason that I said yes is, although I think I was not overly impressed with the study that was done, and some of the outcomes that were shown in the data, I do – and to be honest with you, as a physician, I think I would probably very rarely, if ever, maybe even prescribe it. I do think there is a small number of very difficult to treat patients that, for whatever reason -- and I'm not sure that we totally understand why that is. But there are a small number of patients that are difficult to control, both biochemically and apparently in terms of symptoms, that I think could potentially benefit. And I think it is useful that they at least have this option."

The majority of members remained concerned about the potential risk of osteosarcoma and many of the members who voted no stated that the demonstrated benefit did not outweigh this risk. There was general agreement among members that the risk/benefit of the drug could have been altered had alternative dosing regimens, approximating physiology more closely, been explored in development (twice daily dosing, delayed release dosing, pump dosing etc.)

The committee members who voted "Yes" made the following post-approval recommendations:

- Follow-up safety studies on osteosarcoma

- Studies of a more frequent dosing interval
- Require mandatory reporting of osteosarcoma
- Education of prescribers and patients

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

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

Refer to the full transcript for details of the committee discussion.

10. Pediatrics

Refer to Dr. Roman's and Lowy's reviews for details.

11. Other Relevant Regulatory Issues

Several issues related to good clinical practice violation were identified and are reviewed in Drs. Kleppinger, Lowy and Clark's reviews. These issues did not materially affect overall conclusions. For full discussions refer to these reviews.

12. Labeling

Efficacy and safety issues important for labeling considerations have been discussed in the relevant sections of this memorandum.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

I agree with recommendations made by Drs. Lowy and Roman and recommend approving Natpara as: *an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.*

REPLACE demonstrated that compared to placebo, Natpara was effective in preventing decreases in serum calcium in adult subjects with hypoparathyroidism whose active vitamin D dose had been cut by half at the time of randomization. In patients on Natpara, average serum calcium levels remained within the normal range for 24-weeks despite further reduction in calcium raising drugs (i.e., active vitamin D and oral calcium supplements). Maintenance of serum calcium in this condition is directly linked to symptomatic control as most symptoms associated with hypoparathyroidism are attributed to abnormally low serum calcium. Thus, it is clear that against placebo Natpara is effective at raising serum calcium and would provide a therapeutic benefit to patients with hypoparathyroidism and symptomatic hypocalcemia.

What is less clear from the data in the application is whether Natpara offers a therapeutic advantage over the standard of care (e.g., calcium supplementation and active forms of vitamin D). No advantage of Natpara over the standard of care was documented in terms of; serum calcium levels at the end of 24-weeks, ease of symptomatic control[8], 24-hour urinary calcium excretion, or quality of life[9] in REPLACE. While several patients who testified as having participated in NPS sponsored trials reported drastic improvement in "brain fog" at the open public hearing session of the advisory committee meeting, no clear improvement in the emotional, mental or mental component scores attributable to Natpara were observed on the quality of life instrument used in REPLACE. The fact that Natpara has not been demonstrated to confer an objective advantage over available therapy is an important consideration as Natpara poses a potential serious risk of osteosarcoma and the standard of care does not.

The applicant makes the case that the active ingredient in Natpara is identical to the hormone deficient in the condition and thus ***replaces*** (emphasis added) the deficient hormone. The applicant argues that observed pharmacodynamic changes on bone turnover (i.e., using bone resorption and formation markers) and small decreases in mean serum phosphorus provide evidence of benefit over existing therapies. While these arguments are on their face valid, these biochemial changes, absent outcomes data[10], do not provide substantial evidence of a therapeutic benefit beyond calcium control to justify the additional risk. The effect of intermittent, pulsatile, pharmacologic doses of PTH on bone and other PTH targets are expected to differ substantially from physiologic secretion which is tonic and subject to negative feedback. As discussed above, no benefit in terms of hypercalcemia, hypercalciuria, y and hypocalcemia was noted tolerability. Furthermore, it is unknown whether delivery of pharmacologic doses of PTH intermittently would result in a net benefit to hypoparathyroid bone. Finally, the benefit of the small observed decrease in serum phosphorus may be counterbalanced by a higher calcium levels and may not translate to a

[8] The adverse reaction profile suggested more symptomatic hypercalcemia and hypocalcemia on Natpara than on placebo added to standard of care therapies.
[9] using the SF-36
[10] decrease in fracture, decrease in events of soft tissue calcifications

clinically relevant decrease in extracellular calcification. As experience with insulin in type-1 diabetes shows, pharmacological hormone replacement often falls short of physiology.

Natpara would be expected to offer benefit to patients with hypoparathyroidism who can only control hypocalcemia with large doses of calcium supplementation, multiple times daily, by decreasing pill burden. Patients with hypoparathyroidism in the REPLACE trial and in the largest available published cohort study[11] were controlled with approximately 2000 mg of calcium supplementation per day (1000 mg above the recommended daily allowance for adult patients) and ~75 mcg of 1,25 dihydroxyvitamin D (active vitamin D) per day. A considerable proportion of patients (~42%) were able to eliminate active vitamin D supplementation and reduce calcium supplementation to 500 mg per day in REPLACE. Natpara would reduce pill burden by ~4 pills per day in the average[12] patient but the tradeoff would be the inconvenience of a daily injection.

Even in the absence of a demonstrated advantage over existing therapy, committee members at the Advisory Committee cited experience of having observed, very rarely, patients with hypoparathyroidism who could not be well controlled on available therapies and cited this reason to substantiate their approval recommendations. I concur with this overall view. In the absence of a clearly demonstrated benefit of Natpara over available therapy however, and in light of the potential serious risk of osteosarcoma, I recommend that Natpara be reserved for patients who are not well controlled on available therapies. The demonstration of benefits based on hard outcomes (i.e., fracture rates, renal impairment) is unlikely to be feasible in this orphan population. Demonstrating an effect on 24-hour urinary calcium excretion could be explored in future studies and could potentially change the benefit risk balance favorably.

The major risks identified included; the potential risk of osteosarcoma (discussed in Section 2), and risks associated with over (hypercalcemia) and under (hypocalcemia) dosing. Overall the tolerability profile of Natpara did not suggest an improvement over the standard of care. The risks associated with over and under dosing and mitigation strategies to prevent these risks will be communicated through product labeling.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

In accordance with Section 505-1 of the Food Drug and Cosmetics Act, Natpara will be approved with a REMS with ETASU. Dr. Pippins, Deputy Director for Safety, has summarized the Division's rationale as follows:

"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

[11] Journal of Clinical Endocrinology and Metabolism, December 2012, 97(12):4507–4514
[12] Assumes one pill for active vitamin D and three 500 mg pills for calcium supplements.

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 risk based on nonclinical data, the lack of familiarity with osteosarcoma (a rare cancer) among 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."

- Recommendation for other Postmarketing Requirements and Commitments

Four postmarketing studies/trials for Natpara will be required under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA); A nonclinical study to evaluate the effect of dosing regimens on osteoblast proliferation; an enhanced pharmacovigilance study of osteosarcoma in patients treated with Naptara; a clinical pharmacology trial to assess the pharmacokinetics and pharmacodynamic effect of Natpara dose and dosing regimen on the control of serum calcium and normalization of calcium excretion in urine; and a 26-week clinical trial to evaluate the longer term safety and effect of an alternative dose(s) and/or dosing regimen(s) of Natpara, including longer term safety with respect to hypercalciuria.

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/s/

JEAN-MARC P GUETTIER
01/23/2015