PDL NEW DRUG REVIEW

Proprietary Name: Natpara®
Common Name: parathyroid hormone
PDL Category: Parathyroid Hormones

Comparable Products	Preferred Drug List Status
Calcitriol	Preferred

Summary

Indications and Usage: Adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism. Natpara® was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations, or in those with acute post-surgical hypoparathyroidism. Owing to the potential risk of osteosarcoma, Natpara® is recommended only for those patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone.

This is a pregnancy category C medication. The safety and efficacy of use in children under the age of 18 years have not been established.

Dosage Forms: Multiple dose, dual chamber glass cartridge containing powder and diluent: 25mcg per dose strength (0.40mg for reconstitution with 1.13ml), 50mcg per dose strength (0.80mg for reconstitution with 1.13ml), 75mcg per dose strength (1.21mg for reconstitution with 1.13ml), and 100mcg per dose strength (1.61mg for reconstitution with 1.13ml)

Recommended Dosage: Dosing should be individualized based on total serum calcium (albumin-corrected) and 24-hour urinary calcium excretion. Doses of active forms of vitamin D and calcium supplements will need to be adjusted when using Natpara®. The goal of this treatment is to achieve serum calcium within the lower half of the normal range (i.e. between 8-9mg/dl). Both prior to initiating and during therapy, confirm 25-hydroxyvitamin D stores are sufficient and measure serum calcium to insure a level of >7.5mg/dl before starting treatment.

The recommended dose is the minimum dose needed to prevent both hypocalcemia and hypercalciuria. This dose will typically be the dose that maintains total serum calcium (albumin-corrected) within the lower half of the normal range without needing active forms of vitamin D and with calcium supplementation sufficient and individualized to meet daily needs.

Dosing should be initiated at 50mcg SC in the thigh QD. If using active forms of vitamin D, decrease the dose of the vitamin D by 50% if serum calcium is >7.5mg/dl. Maintain calcium supplement dose. Measure serum calcium within 3-7 days, and adjust the dose of active Vitamin D, calcium, or both per the measured value of calcium. Repeat obtaining calcium levels and adjustment of dose until serum calcium levels are within the lower half of the normal range, active vitamin D has been discontinued, and calcium supplementation is enough to meet daily requirements. Suggested adjustments are illustrated in the table below, which was adapted from the prescribing information.

	Adjust first	Adjust second
Serum Calcium	**Active Vitamin D forms**	**Calcium supplement**
>Upper limit of normal (10.6mg/dl)	↓ or discontinue*	↓
> than 9mg/dl AND BELOW the upper limit of normal (10.6mg/dl)	↓ or discontinue*	No change or ↓ if active vitamin D been discontinued
≤ 9mg/dl AND ABOVE 8mg/dl	No change	No change
Lower than 8mg/dl	Increase	Increase
*Discontinue in patients receiving the lowest available dose		

Natpara® dose increases may be performed every 4 weeks up to a maximum dosage of 100mcg daily if serum calcium cannot be maintained at >8mg/dl without an active form of vitamin D and/or oral calcium supplementation. Monitor clinical response and serum calcium level after Natpara® dose adjustment, and adjust active vitamin D and calcium supplements as above.

Dose adjustments are not recommended in patients with mild or moderate hepatic impairment. Studies did not include sufficient numbers of subjects with moderate or severe renal impairment to assess response.

Drug Interactions: It is recommended to monitor serum calcium and digoxin levels in those using digoxin concomitantly with Natpara®. Adjust the dose of either as needed. Concomitant use of Natpara® with alendronate is not recommended.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Natpara®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than placebo.* The most frequently reported adverse events included paraesthesia (6%), hypocalcemia (4%), headache (2%), hypercalcemia (16%), nausea (0%), hypoesthesia (4%), diarrhea (9%), vomiting (12%), arthralgia (1%), hypercalciuria (3%), pain in extremity (2%), upper respiratory tract infection (3%), abdominal pain upper (4%), sinusitis (2%), blood 25-hydroxycholecalciferol decreased (3%), hypertension (1%), hypoesthesia facial (3%), neck pain (3%), albumin-corrected serum calcium >10.6 to ≤12mg/dl (30% during titration period and 10% during maintenance), albumin-corrected serum calcium >12 to ≤13mg/dl (2% during titration period and 0% during maintenance), albumin-corrected serum calcium ≥7 to <8.4mg/dl (0% during titration and 0% during maintenance), and albumin-corrected serum calcium <7mg/dl (0% during titration period and 12% during maintenance).

Natpara® has a box warning regarding the potential risk of osteosarcoma with use. The occurrence of osteosarcoma was dependent on parathyroid hormone dose and treatment duration in male and female rats. Due to this potential risk, Natpara® should only be used in patients who cannot be well-controlled on calcium and active forms of vitamin D alone and for whom the potential benefits outweigh the potential risks. Use should be avoided in those who are at increased baseline risk for osteosarcoma, such as those with Paget's disease of bone. Last, due to the risk of osteosarcoma, Natpara® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Natpara® REMS program. With this program, only certified healthcare providers can prescribe and only certified pharmacies can dispense Natpara®. Additional information can be found at www.NATPARAREMS.com.

Contraindications: None

Manufacturer: NPS Pharmaceuticals, Inc

Analysis: Parathyroid hormone, the active ingredient of Natpara®, is made by recombinant DNA technology using a modified strain of *Escherichia coli*. Parathyroid hormone raises serum calcium by increasing renal tubular calcium

reabsorption, increasing intestinal calcium absorption, and by increasing bone turnover which releases calcium into circulation.

One randomized, double-blind, placebo-controlled 24 week study was performed to assess the safety and efficacy of Natpara® in adults with established hypoparathyroidism receiving calcium and active forms of vitamin D. Before randomization, a 2 to 16 run-in phase was initiated where calcium supplementation and vitamin D doses were adjusted to target serum calcium between 8-9mg/dl. Adults were then randomized to Natpara® or placebo and this was followed by a 12-week titration phase and 12-week maintenance phase. The primary outcome was the proportion of responders at the end of treatment, with response defined as individuals who had: ≥50% reduction from baseline in the dose of active vitamin D, ≥50% reduction from baseline in the dose of oral calcium supplementation, and an albumin-corrected total serum calcium level between 7.5-10.6mg/dl.

Results suggested that at the end of treatment, a significantly greater number in the Natpara® group (54.8%) met the response criteria as compared to the placebo group (2.5%; $p<0.001$). Furthermore, significantly more in the Natpara® group (42%) were independent of active forms of vitamin D and were on no more than 500mg of oral calcium as compared with placebo (2.5%; $p<0.001$). Significant differences in the proportion with a calcium level between 7.5-10.6mg at the end of treatment were not seen between Natpara® and placebo.

Place in Therapy: Parathyroid hormone is one of the primary hormones that control serum calcium (along with vitamin D). Hypoparathyroidism occurs when the parathyroid glands are damaged (autoimmune, surgical), abnormal parathyroid gland development, altered regulation of parathyroid hormone production, or impaired parathyroid hormone action. One noted reference source suggests initially using calcium and vitamin D supplementation for control of chronic hypoparathyroidism. The authors note that adding recombinant parathyroid hormone may be an option for those patients who cannot maintain stable serum calcium levels with calcium and vitamin D supplementation. While it is noted that SC parathyroid hormone is effective, "....it is not yet initial therapy because of high cost, the necessity for subcutaneous administration, and the uncertainty about long-term safety of dosing for primary hypoparathyroidism."[2]

Natpara® should remain non-preferred and require prior authorization to assess diagnosis and prior trials of preferred agents.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

References

[1] Natpara [package insert]. Bedminster, NJ: NPS Pharmaceuticals, Inc; 2015.

[2] UpToDate desktop version. Hypoparathyroidism. Accessed May 2015.