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Natpara (parathyroid hormone) Prior Authorization with Quantity Limit Program Summary

FDA APPROVED INDICATIONS AND DOSAGE[1]

Agent	Indication	Dosing and Administration
Natpara® (parathyroid hormone) subcutaneous injection	Indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism	Initial dose: 50 mcg injected once daily in the thigh. When starting Natpara, decrease dose of active vitamin D by 50%, if serum calcium is above 7.5 mg/dL. Maintenance dose: The dose may be increased by 25 mcg every 4 weeks up to a maximum daily dose of 100 mcg daily if serum calcium cannot be maintained above 8 mg/dL without an active form of vitamin D and/or oral calcium supplementation. The dose of Natpara should be individualized to achieve a serum calcium level in the lower half of the normal range (8-9 mg/dL).

Limitations of Use:
- Because of the potential risk of osteosarcoma, Natpara is recommended only for patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone.
- Natpara was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations.
- Natpara was not studied in patients with acute post-surgical hypoparathyroidism.

CLINICAL RATIONALE

Hypoparathyroidism is a rare disorder or mineral metabolism characterized by hypocalcemia and absent or deficient production of parathyroid hormone (PTH). PTH is one of the major hormones that regulate calcium along with vitamin D via direct effects on the bone and kidney and indirect effects on the gastrointestinal tract. Hypoparathyroidism occurs when there is destruction of the parathyroid glands (autoimmune, surgical), abnormal parathyroid gland development, altered regulation of PTH production, or impaired PTH action. When PTH secretion is insufficient, hypocalcemia develops.[2,3] Hypocalcemia due to hypoparathyroidism may be associated with a spectrum of clinical manifestations, ranging from few if any symptoms, if the hypocalcemia is mild, to life-threatening seizures, refractory heart failure, or laryngospasm if it is severe.[3] Hypocalcemia can affect the function of most organs, but in hypoparathyroidism, the most obvious organ systems that become dysfunctional are neurological, cognitive, muscular, and cardiac.[2]

Goals of therapy in patients with hypoparathyroidism are to relieve symptoms, to raise and maintain the serum calcium concentration to the low-normal range (e.g. 8.0 to 8.5 mg/dL

or 2.0 to 2.1 mmol/L), and to prevent iatrogenic development of kidney stones.[3] Treatment with oral calcium supplements and active forms of Vitamin D (calcitriol, cholecalciferol, or ergocalciferol) is the current standard of care.[2,3] Monitoring of urinary and serum calcium and serum phosphate is required weekly initially, until a stable serum calcium concentration is achieved. Thereafter, monitoring levels at 3 to 6 month intervals is sufficient.[3] These patients lack the normal stimulatory effect of PTH on renal tubular calcium reabsorption, therefore excrete more calcium than normal patients at the same serum calcium concentration. Urinary calcium excretion should but measured periodically and dose of calcium and vitamin D reduced if it is elevated (≥300 mg [7.6 mmol] in 24 hours). Some patients may require the addition of thiazide diuretics with or without dietary sodium restrictions to decrease urinary calcium excretion. Second line therapy is recombinant human PTH.[3]

Efficacy[2]

- Efficacy of PTH was evaluated in a 24-week, randomized, double-blind, placebo-controlled, multicenter trial (REPLACE3). In this trial, patients with established hypoparathyroidism receiving calcium and active forms of vitamin D (vitamin D metabolite or analogs) were randomized to PTH (n=84) or placebo (n=40).
- 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 calcium concentration between 8.0 and 9.0 mg/dL and 25-hydroxyvitamin D was replaced in patients with insufficient stores. At randomization, baseline serum calcium was 8.6 mg 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 0.75 mcg (0.5, 1) of calcitriol.
- For the efficacy analysis, patients that fulfilled three components of a three-part response criterion were considered responders. A responder was defined as an individual 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 concentration between 7.5 mg/dL and 10.6 mg/dL.
- At the end of treatment, significantly (p-value <0.001) more patients treated with PTH (54.8%) vs. placebo (2.5%) met the response criterion. Forty-two percent of patients randomized to PTH were independent of active forms of vitamin D and were on < 500 mg of oral calcium, compared with 2.5% of patients randomized to placebo (p<0.001). There were no differences in the proportion of patients with a calcium level between 7.5 mg and 10.6 mg at end of treatment between patients randomized to PTH and placebo.

Safety[2]

- Boxed Warning- Risk of Osteosarcoma: In male and female rats, PTH caused an increase in incidence of osteosarcoma, with occurrence dependent on PTH dose and treatment duration. This effect was observed at PTH levels from 3 to 71 times those in humans receiving a 100 mcg dose of PTH. Data could not exclude a risk to humans Due to risk of osteosarcoma, PTH should be used only in patients not controlled on calcium and active vitamin D alone and for whom potential benefits outweigh risks. Avoid use in patients at increased baseline risk for osteosarcoma (e.g., Paget's disease of bone, elevated alkaline phosphatase, open epiphyses, predisposition to osteosarcoma, or history of external beam or implant radiation therapy involving the skeleton).
- Co-administration of alendronate and Natpara leads to reduction in the calcium sparing effect, which can interfere with the normalization of serum calcium. Concomitant use of Natpara with alendronate is not recommended.

REFERENCES

1. Natpara prescribing information. Shire-NPS Pharmaceuticals, Inc. July 2016.
2. Brandi, Maria Luisa, et al. Management of Hypoparathyroidism: Summary Statement and Guidelines. *J Clin Endocrinol Metab*. June 2016. 101(6):2273-2283.
3. Goltzman, David, MD, et al. Hypoparathyroidsim. UpToDate. Last updated October 2017. Literature review current through July 2018.

Natpara Prior Authorization with Quantity Limit

OBJECTIVE
The intent of the Natpara Prior Authorization (PA) Program is to encourage appropriate selection of patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies. Criteria will approve doses that are at or below the maximum FDA labeled dose. Doses above the program set limit will be approved if the requested quantity is below the FDA limit and cannot be dose optimized. When the quantity is above the FDA limit, the prescriber must submit documentation in support of therapy for the higher dose for the intended diagnosis.

TARGET AGENT
Natpara® (parathyroid hormone)

Brand (generic)	GPI	Multisource Code	Quantity Limit
Natpara (parathyroid hormone)			
25 mcg	3004405510E110	M, N, O, or Y	1 package of 2 cartridges/28 days
50 mcg	3004405510E120	M, N, O, or Y	1 package of 2 cartridges/28 days
75 mcg	3004405510E130	M, N, O, or Y	1 package of 2 cartridges/28 days
100 mcg	3004405510E140	M, N, O, or Y	1 package of 2 cartridges/28 days

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Natpara will be approved when the following are met:

1. ONE of the following:
    A. The patient has the diagnosis of hypocalcemia associated with hypoparathyroidism AND ALL of the following:
        i. The patient has baseline vitamin D levels above the lower limit of normal
        AND
        ii. The patient has baseline serum calcium levels above 7.5 mg/dL
        AND
        The patient has had an inadequate response to maximally tolerated calcium AND vitamin D supplements (e.g., calcitriol, ergocalciferol, cholecalciferol)
        AND
        iii. The patient will continue calcium and vitamin D supplementation with the requested agent
        AND
        iv. The patient does NOT have hypoparathyroidism caused by calcium-sensing receptor mutations
        AND

v. The patient does NOT have acute post-surgical hypoparathyroidism

OR

B. The patient has another FDA approved indication for the requested agent

AND

2. The patient is NOT at an increased 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)

AND

3. ONE of the following:
   A. The patient is NOT currently being treated with alendronate

   OR

   B. The patient is currently being treated with alendronate AND will discontinue prior to initiating the requested agent

AND

4. The prescriber is a specialist (e.g. endocrinologist) in the area of the patient's diagnosis or the prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

5. The patient does NOT have any FDA labeled contraindication(s) to the requested agent

AND

6. ONE of the following:
   A. The requested quantity (dose) is NOT greater than the program quantity limit

   OR

   B. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit

      AND

      ii. The requested quantity (dose) is less than or equal to the maximum FDA labeled dose

      AND

      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

   OR

   C. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit

      AND

      ii. The requested quantity (dose) is greater than the maximum FDA labeled dose

      AND

      iii. The prescriber has submitted documentation in support of therapy with a higher dose for the requested indication

Length of Approval: 6 months

Renewal Evaluation

Natpara will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the Prime Therapeutics Prior Authorization process
   AND
2. If the patient has a diagnosis of hypocalcemia associated with hypoparathyroidism, then ALL of the following:
   A. The patient has had a 50% reduction from baseline in the dose of calcium supplementation
      AND
   B. The patient has had a 50% reduction from baseline in the dose of vitamin D supplementation
      AND
   C. The patient has an albumin-corrected total serum calcium concentration between 7.5 mg/dL and 10.6 mg/dL
      AND
   D. The patient will continue with calcium and vitamin D supplementation with the requested agent

   AND
3. The patient is NOT at an increased 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)
   AND
4. ONE of the following:
   A. The patient is NOT currently being treated with alendronate
      OR
   B. The patient is currently being treated with alendronate AND will discontinue prior to continuing the requested agent

   AND
5. The prescriber is a specialist in the area of the patient's diagnosis (e.g. endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis
   AND
6. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
   AND
7. ONE of the following:
   A. The requested quantity (dose) is NOT greater than the program quantity limit
      OR
   B. ALL of the following
      i. The requested quantity (dose) is greater than the program quantity limit
         AND
      ii. The requested quantity (dose) is less than or equal to the maximum FDA labeled dose
         AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

      OR
   C. ALL of the following:

i. The requested quantity (dose) is greater than the program quantity limit
AND
ii. The requested quantity (dose) is greater than the maximum FDA labeled dose
AND
iii. The prescriber has submitted documentation in support of therapy with a higher dose for the requested indication

Length of Approval: 12 months