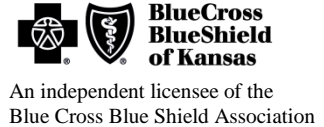


Medical Policy



Title: Natpara (parathyroid hormone)

- Prime Therapeutics will review Prior Authorization requests.

Prior Authorization Form:

<http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6197KS-NATP.pdf>

Link to Drug List (Formulary):

<https://www.bcbsks.com/drugs/>

Professional

Original Effective Date: November 1, 2015
Revision Date(s): November 1, 2015;
January 1, 2016; April 1, 2016;
February 1, 2017; January 1, 2018
Current Effective Date: February 1, 2017

Institutional

Original Effective Date: November 1, 2015
Revision Date(s): November 1, 2015;
January 1, 2016; April 1, 2016;
February 1, 2017; January 1, 2018
Current Effective Date: February 1, 2017

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact [Blue Cross and Blue Shield of Kansas Customer Service](#).

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

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 Drug

- **Natpara** (parathyroid hormone)

FDA Approved Indications and Dosage²

Available Product	Indication	Dosing and Administration
Natpara (parathyroid hormone)	Natpara is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism	<ul style="list-style-type: none"> ▪ The starting dose of Natpara is 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. ▪ 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). ▪ The dose may be increased by 25 mcg every 4 weeks up to a maximum daily dose of 100 mcg daily.

Limitations of Use:

1. 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.
2. Natpara was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations.
3. Natpara was not studied in patients with acute post-surgical hypoparathyroidism.

*Severe hypocalcemia can occur with abrupt interruption or discontinuation of Natpara.

POLICY**Prior Authorization and Quantity Limits Criteria for Approval**

Natpara (parathyroid hormone) – INITIAL evaluation will be approved when the following are met:

1. The patient does not have any FDA labeled contraindication(s) to the requested agent
AND
2. One of the following:
 - A. The patient has the diagnosis of hypocalcemia with hypoparathyroidism and ALL of the following:
 - i. The prescriber has confirmed the patient's 25-hydroxyvitamin D stores are sufficient
AND
 - ii. The prescriber has confirmed the patient's serum calcium is above 7.5 mg/dL
AND
 - iii. The patient cannot be well-controlled on maximally tolerated calcium supplements and active forms of vitamin D (vitamin D metabolite or analogs): e.g., calcitriol, ergocalciferol, cholecalciferol) alone
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 diagnosis
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 on concomitant use of alendronate
OR
 - B. The patient is currently on alendronate and will discontinue it prior to therapy with Natpara
AND

5. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist) or the prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis
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 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 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 FDA labeled dose
AND
 - iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Approval: 6 months

Renewal Evaluation will be approved when ALL of the following are met:

1. The patient has been approved for the requested agent previously through the Prime Therapeutics PA process
AND
2. The patient does not have any FDA labeled contraindication(s) to the requested agent
AND
3. If hypocalcemia with hypoparathyroidism ALL of the following:
 - A. The patient has had a 50% reduction from baseline in the dose of oral calcium supplementation
AND
 - B. The patient has had a 50% reduction from baseline in the dose of active vitamin D supplementation (vitamin D metabolite or analogs)
AND

- C. The patient has an albumin-corrected total serum calcium concentration between 7.5 mg/dL and 10.6 mg/dL

AND

4. 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

5. ONE of the following:

- A. The patient is not on concomitant use of alendronate

OR

- B. The patient is currently on alendronate and will discontinue it prior to therapy with Natpara

AND

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

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 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 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 FDA labeled dose

AND

- iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Approval: 12 months

Agent	Contraindication(s)
Natpara (parathyroid hormone)	None

Quantity Limits	
Brand (generic)	Quantity per 28 Day Limit
Natpara (parathyroid hormone)	
25 mcg	14 packages of 2 cartridges / 28 days
50 mcg	14 packages of 2 cartridges / 28 days
75 mcg	14 packages of 2 cartridges / 28 days
100 mcg	14 packages of 2 cartridges / 28 days

RATIONALE¹

Hypoparathyroidism is a rare disorder given orphan disease designation by the U.S. Food and Drug Administration. Hypoparathyroidism is a rare disease affecting about 60,000 individuals in the U.S, resulting from parathyroid gland hypofunction, characterized by low or normal circulating parathyroid hormone (PTH) levels in the setting of hypocalcemia. Hypoparathyroidism is often due to inadvertent removal of parathyroid glands during thyroidectomy or due to autoimmune or congenital diseases. PTH secretion from the parathyroid glands is controlled by 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, and bone turnover, releasing calcium from bone. These PTH effects will raise circulating calcium levels until calcium concentration is sufficiently high to return PTH secretion to baseline levels. Symptoms are related to hypocalcemia (numbness, paresthesia, musculoskeletal irritability, seizures, cardiac arrhythmias, laryngeal spasms) and complications due to chronic hypocalcemia (cardiomyopathy), chronically elevated phosphorus levels (extracellular calcification), low bone turnover (increased bone mass and fragility) and chronic hypercalciuria (nephrocalcinosis, nephrolithiasis, renal impairment).

Treatment with oral calcium supplements and active forms of Vitamin D is the current standard of care.³ The goal of therapy is to correct low calcium levels, prevent hypocalcemia, minimize hypercalciuria, and minimize risk of extracellular calcification. Needs are not currently met by the available standard of care treatment. Adjustment of serum calcium using supplemental calcium and vitamin D is imprecise. Under-treatment results in acute or chronic hypocalcemia. Overtreatment results in hypercalcemia and hypercalciuria. Patients must ingest oral calcium supplements multiple times daily and may not be able to tolerate large calcium doses due to side effects (e.g., constipation). Current therapies do not address underlying renal calcium handling or bone turnover abnormalities due to parathyroid gland malfunction.

Efficacy²

- 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 weeks 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.

Safety²

- **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.

REVISIONS

11-01-2015	Policy added to the bcbsks.com web site on 09-16-2015, effective 11-01-2015.
01-01-2016	Policy published 01-15-2016. Policy retro-effective to 01-01-2016. <ul style="list-style-type: none"> ▪ Policy reviewed with no changes to content. ▪ Updated policy format from "C i 1, 2, 3, 4, 5" to "C i a, b, c, d, e"
04-01-2016	Published 05-11-2016. Retro-effective to 04-01-2016. <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ Corrected Quantity Limits for 25 mcg, 50 mcg, 75 mcg, 100 mcg from "14 packages" to "1 package" to read "1 package of 2 cartridges/28 days"
02-01-2017	In Policy section: <ul style="list-style-type: none"> ▪ Removed "A. There is documentation that the patient is currently receiving the target agent OR B. The prescriber states the patient is using the target agent AND is at risk if therapy is changed C. ONE of the following:" <ul style="list-style-type: none"> ▪ In Item 2 A c added "e.g., calcitriol, ergocalciferol, cholecalciferol)" to read "The patient cannot be well-controlled on maximally tolerated calcium supplements and active forms of

	vitamin D (vitamin D metabolite or analogs): e.g., calcitriol, ergocalciferol, cholecalciferol) alone" <ul style="list-style-type: none"> ▪ Updated Quantity Limits chart
	Rationale section updated
	References updated
01-01-2018	Policy reviewed with no changes.
	References updated

REFERENCES

1. CDER. FDA. Summary Review. Natpara. Parathyroid hormone. NDA 125511. January 2015.
2. Natpara prescribing information. July 2016.
3. Bollerslev J., Rejnmark L, et al. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol August 1, 2015. 173 G1-G20.