Original Effective Date: 04/01/2019
Current Effective Date: 09/20/2023
Last P&T Approval/Version: 07/26/2023
Next Review Due By: 07/2024
Policy Number: C16013-A

Natpara (parathyroid hormone)

PRODUCTS AFFECTED

Natpara (parathyroid hormone)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Hypocalcemia with hypoparathyroidism

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. HYPOCALCEMIA WITH HYPOPARATHYROIDISM:
   1. Documented diagnosis of hypocalcemia with hypoparathyroidism
      AND
   2. Documentation that member's 25-hydroxyvitamin D stores are sufficient (>50 nmol/L to < 75 nmol/L

are considered adequate in normal healthy patients)
AND

3. Documentation member's serum calcium is above 7.5 mg/dL
AND
4. Documentation of trial and failure of maximally tolerated calcium supplements and active forms of vitamin D (vitamin D metabolite or analogs: e.g., calcitriol, ergocalciferol, cholecalciferol) alone. Documentation of medication(s) tried and maximally tolerated dosing required.
AND
5. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Natpara (parathyroid hormone) include: hypersensitivity to any component of the product, patients at an increased risk for osteosarcoma which includes 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
6. Prescriber attests member is not on concomitant alendronate OR is currently on alendronate and will discontinue it prior to therapy with Natpara

CONTINUATION OF THERAPY:

A. HYPOCALCEMIA WITH HYPOPARATHYROIDISM:

1. Prescriber attests the member continues to take calcium supplementation sufficient to meet daily requirements
AND
2. Documentation the member has had a 50% reduction from baseline in the dose of active vitamin D supplementation (vitamin D metabolite or analogs)
AND
3. Documentation member has an albumin-corrected total serum calcium concentration between 7.5 mg/dL and 10.6 mg/dL
AND
4. Prescriber attests the member 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. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)
AND
6. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with an endocrinologist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

18 years of age and older

QUANTITY:

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.
Maximum Quantity Limits – 1 box per 28 days

PLACE OF ADMINISTRATION:
The recommendation is that injectable medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Subcutaneous

DRUG CLASS:
Parathyroid Hormone and Derivatives

FDA-APPROVED USES:
Indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.
Limitations of Use: Natpara is recommended only for patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone due potential risk of osteosarcoma. 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.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Natpara (parathyroid hormone) is a hormonal injection administered once daily that helps to regulate the body's calcium levels. Natpara is used as add-on therapy to manage hypocalcemia of hypoparathyroidism in patients who do not respond to calcium and vitamin D alone. It works by raising serum calcium through increased tubular reabsorption, increased intestinal absorption and increased bone turnover. Hypoparathyroidism is caused by loss of function of the parathyroid glands and occurs most commonly as a result of surgical removal of the parathyroid glands and more rarely as a result of autoimmune or congenital diseases. 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, and 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.

Efficacy

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. Safety 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.

Natpara REMS

Because of the potential risk of osteosarcoma associated with NATPARA therapy, NATPARA is available only through a restricted REMS program called the NATPARA REMS Program. Under the NATPARA REMS Program, only certified healthcare providers can prescribe and only certified pharmacies can dispense NATPARA. Further information is available at www.NATPARAREMS.com or by telephone at 1-855-NATPARA (1-855-628-7272).

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Natpara (parathyroid hormone) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Natpara (parathyroid hormone)

include: hypersensitivity to any component of the product, patients at an increased risk for osteosarcoma which includes 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.

OTHER SPECIAL CONSIDERATIONS:
Natpara has an FDA labeled Black Box Warning for potential risk of osteosarcoma. In male and female rats, parathyroid hormone caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. A risk to humans could not be excluded. 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). NATPARA is available only through a restricted program called the NATPARA REMS Program.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Natpara CART 25MCG, 50MCG, 75MCG, 100MCG (1 box= 2 cartridges)

*Currently a recall on all doses as of 9/5/2019
*** Updated 3/31/2021: The manufacturing delay that is currently affecting NATPARA 100mcg within the SUP has further impacted the manufacturer's timelines. SUP-enrolled patients **currently** receiving Natpara 25 mcg, 50 mcg, or 75 mcg are not impacted by supply interruption at this time. The manufacturer anticipates an interruption in supply of the 100-mcg strength. The manufacturer will keep the community informed of relevant updates as they progress, and at this time they do not expect a return to market before March 31, 2022. (https://www.takeda.com/496906/siteassets/en-us/home/newsroom/natpara-recall/haopenletter_3-31-21.pdf)
***Updated 10/4/2022: Takeda will discontinue manufacturing Natpara globally at the end of 2024 due to unresolved supply issues that are specific to the product. As a result, Takeda will not re-commercialize Natpara in the U.S. Until the end of 2024, Takeda's key priority is to maintain treatment continuity for patients who are currently receiving Natpara, subject to available supply. This includes those enrolled in the U.S. Special Use Program.

REFERENCES

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Quantity Background Available Dosage Forms References	Q3 2023
REVISION- Notable revisions: Required Medical Information Contraindications/Exclusions/Discontinuation Other Special Considerations	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file