

Recombinant human parathyroid hormone 1-84 (Natpara)**Criteria for Use****May 2016**

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vawww.pbm.va.gov> for further information.

Exclusion Criteria If the answer to ANY item below is met, then the patient should NOT receive Recombinant human parathyroid hormone 1-84 (rhPTH 1-84).

- Diagnosis of permanent hypoparathyroidism has not been confirmed.(i.e. acute post-surgical hypoparathyroidism)
- Paget's disease of the bone, elevations of alkaline phosphatase of unknown etiology, patients with open epiphyses, hereditary disorders causing a predisposition to osteosarcoma, prior history of external beam or implant radiation therapy involving the skeleton.
- Hypoparathyroidism due to calcium-sensing receptor mutations (i.e. autosomal dominant hypocalcemia (ADH))
- Concurrent use of alendronate or other bisphosphonate

Inclusion Criteria The answers to all of the following must be fulfilled in order to meet criteria.

- Treatment initiated and followed by a VA Endocrinologist experienced in the diagnosis and management of hypoparathyroidism and certified to prescribe recombinant human parathyroid hormone (rhPTH 1-84).
- Diagnosis of hypoparathyroidism (PTH concentration that is undetectable or inappropriately low (i.e. ≤ 20 pg/mL) in the presence of hypocalcemia on at least two occasions).
- Inability to maintain the albumin corrected serum calcium with frequent episodes of hypo- and/or hypercalcemia with traditional medical management (i.e. oral supplementation with calcium and active vitamin D, as well as thiazide diuretic use)
- For women of childbearing potential, pregnancy should be excluded prior to receiving rhPTH 1-84 and the patient provided contraceptive counseling on potential risk vs. benefit of taking rhPTH 1-84 if patient was to become pregnant.
- All required steps for REMS requirements as listed at: <http://www.natpararems.com/>

Dosage and Administration *Refer to the package insert for additional information

Dosing of rhPTH 1-84 by subcutaneous injection should be individualized based on the total corrected serum calcium and 24-hour urine calcium excretion. The minimum dose to prevent hypocalcemia and hypercalcuria is recommended. This dose is in most cases, the one that maintains serum calcium between 8 and 9 mg/dL without supplementation or use of active forms of vitamin D and is sufficient to meet the patient's daily requirements.

Before beginning rhPTH 1-84, sufficient stores of 25-hydroxy vitamin D should be confirmed. In addition, the total corrected serum calcium must greater than 7.5 mg/dL prior to initiating rhPTH 1-84.

Administer rhPTH 1-84 by subcutaneous injection in the thigh (alternating thighs daily):

Initial Dosing: 50 mcg

- If total corrected serum calcium is greater than 7.5 mg/dL and the patient is on active forms of vitamin D, the active vitamin D dose should be reduced by 50%.
- If the patient is using calcium supplementation, the dose of calcium should be maintained.
- Either the dose of active vitamin D and/or the calcium supplement dose should be adjusted based on the serum calcium level obtained during this interval and the clinically correlated symptoms provided by the manufacturer in the package insert.

Dose Adjustments

- The dose may be adjusted in 25 mcg increments every 4 weeks with a maximum of 100 mcg per dose if the total serum calcium cannot be maintained at a level greater than 8 mg/dL without the use of active vitamin D and/or calcium supplementation.
- If total serum calcium is greater than 9 mg/dL on multiple occasions after discontinuation of active vitamin D and calcium

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Updated versions may be found at <http://www.pbm.va.gov> or <https://vawww.cmopnational.va.gov/cmop/PBM/default.aspx>

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supplementation has been reduced to the amount adequate to meet daily requirements, the dose of rhPTH 1-84 may be reduced to 25 mcg per day.

Maintenance Dosing

- Maintenance dosing should be the minimum rhPTH 1-84 dose required to maintain total corrected serum calcium between 8 and 9 mg/dL, without the use of active forms of vitamin D and with the use of calcium supplementation adequate to meet daily requirements.

Interruption or Discontinuation

- Severe hypocalcemia may result from abrupt interruption or discontinuation of rhPTH 1-84.
- Active vitamin D and supplementation with calcium should be resumed or the doses should be increased, if indicated when patients interrupt or discontinue rhPTH 1-84.

Missed Dose

- If a dose of rhPTH 1-84 is missed, it should be administered as soon as possible and if hypocalcemia occurs, exogenous calcium should be taken.

Monitoring

- Evaluation of renal function should occur prior to and periodically during rhPTH 1-84 therapy.
- A serum calcium level should be obtained between 3 and 7 days following initiation of rhPTH 1-84.
- After any dose adjustments, clinical response and serum calcium should be monitored.
- During interruption or discontinuation, serum calcium as well as signs and symptoms of hypocalcemia should be monitored
- The manufacturer does not provide any specified interval for monitoring. However, a treatment guideline from the European Society of Endocrinology recommends monitoring calcium, magnesium, phosphate, creatinine, and assessment of symptoms of hypo and hypercalcemia at regular intervals, such as every 3-6 months. In addition, monitoring the 24-hour urinary calcium excretion at a regular interval, such as yearly or every other year.
- Following dose changes, weekly or every other week laboratory monitoring is recommended.

Issues for Consideration

- **Indication:** rhPTH 1-84 is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism. rhPTH 1-84 was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations. rhPTH 1-84 was not studied in patients with acute post-surgical hypoparathyroidism.
- **Osteosarcoma risk:** Because of the potential risk of osteosarcoma, rhPTH 1-84 is recommended only for patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone.
- **Hypercalcemia:** Severe hypercalcemia has been reported. The risk is highest when starting or titrating the dose of rhPTH 1-84. Two patients in the rhPTH 1-84 group in one of the clinical trials required IV fluid administration due to hypercalcemia.
- **Hypocalcemia:** Severe hypocalcemia has been reported. The risk is highest when rhPTH 1-84 is withheld, missed, or stopped suddenly. However, hypocalcemia is possible at any time.
- **Risk of Digoxin Toxicity with Concurrent Use of Digitalis Compounds:** Calcium levels affect inotropic effects of digoxin and hypercalcemia may increase the risk of digoxin toxicity with concurrent use.

Renewal Criteria

- Documented compliance with rhPTH 1-84 and monitoring requirements
- Documentation of appropriate renewal dose based upon a recent corrected calcium level (i.e. within one month)
- Followed by a VA Endocrinologist experienced in the diagnosis and management of hypoparathyroidism and certified to prescribe recombinant human parathyroid hormone (rhPTH 1-84).

References

1. Natpara® (Recombinant human parathyroid hormone 1-84) [prescribing information]. Bedminster, NJ: NPS Pharmaceuticals, Inc.; January, 2015. <https://www.natpara.com/prescribing-information/PDF>. Accessed November 10, 2015.
2. Bollerslev J, Rejnmark L, Marcocci C, et al. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. *Eur J Endocrinol* 2015;173, G1–G20
3. Shoback DM, Bilzikian JP, Costa AG, et al. Presentation of Hypoparathyroidism: Etiologies and Clinical Features. *J Clin Endocrinol Metab* 2016. doi: 10.1210/jc.2015-3909.

4. Maria Luisa Brandi ML, Bilezikian JP, Shoback DM, et al. Management of Hypoparathyroidism: Summary Statement and Guidelines. Presentation of Hypoparathyroidism: Etiologies and Clinical Features. J Clin Endocrinol Metab 2016. Doi: 10.1210/jc.2015-3907.

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