

Dosing and Administration Guide for once-daily NATPARA[®] (parathyroid hormone) for Injection

Indications and Usage

NATPARA is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.

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.

Important Safety Information

WARNING: 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.

For more information about the Natpara REMS program, call 1-855-NATPARA or go to www.NATPARAREMS.com.

Please see Important Safety Information on last two pages.

Please see [Full Prescribing Information](#), including Boxed Warning for potential risk of osteosarcoma.

Dosing guidelines for NATPARA¹

Before initiating NATPARA and during treatment with NATPARA

- Confirm 25-hydroxyvitamin D stores are sufficient. If insufficient, replace to sufficient levels per standard of care
- Confirm serum calcium is above 7.5 mg/dL before starting NATPARA

INITIATE NATPARA

- 1 Initiate NATPARA 50 mcg once daily as a subcutaneous injection in the thigh (alternate thigh every day)
- 2 In patients using active forms of vitamin D, decrease the dose of active vitamin D by 50%, if serum calcium is above 7.5 mg/dL
- 3 In patients using calcium supplements, maintain calcium supplement dose
- 4 Measure serum calcium concentration within 3 to 7 days

ADJUST VITAMIN D & CALCIUM

- 5 Adjust dose of active vitamin D or calcium supplement or both based on serum calcium value and clinical assessment (ie, signs and symptoms of hypocalcemia or hypercalcemia). Suggested adjustments to active vitamin D and calcium supplement based on serum calcium levels are shown in the table below
- 6 Repeat steps 4 and 5 until target serum calcium levels are within the lower half of the normal range, active vitamin D has been discontinued, and calcium supplementation is sufficient to meet daily requirements

	ADJUST FIRST	ADJUST SECOND
Serum Calcium	Active Vitamin D Forms	Calcium Supplement
Above the Upper Limit of Normal (10.6 mg/dL)	Decrease or Discontinue*	Decrease
Greater than 9 mg/dL and below the Upper Limit of Normal (10.6 mg/dL)	Decrease or Discontinue*	No change or decrease if active vitamin D has been discontinued
Less than or equal to 9 mg/dL and above 8 mg/dL	No change	No change
Lower than 8 mg/dL	Increase	Increase

*Discontinue in patients receiving the lowest available dose.

Interruption or Discontinuation

Abrupt interruption or discontinuation of NATPARA can result in severe hypocalcemia. Resume treatment with, or increase the dose of, an active form of vitamin D and calcium supplements if indicated in patients interrupting or discontinuing NATPARA, and monitor for signs and symptoms of hypocalcemia and serum calcium levels. In the case of a missed dose, the next NATPARA dose should be administered as soon as reasonably feasible and additional exogenous calcium should be taken in the event of hypocalcemia. **For full dosage and administration instructions, please see the full Prescribing Information section 2.**

Please see Important Safety Information on last two pages.

Please see [Full Prescribing Information](#), including Boxed Warning for potential risk of osteosarcoma.

TITRATE DOSAGE

- The dose of NATPARA may be increased in increments of 25 mcg every 4 weeks, up to a maximum daily dose of 100 mcg 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 may be decreased to as low as 25 mcg per day if total serum calcium is consistently above 9 mg/dL after the active form of vitamin D has been discontinued and calcium supplement has been decreased to a dose sufficient to meet daily requirements

REMEMBER: After a NATPARA dose change, monitor clinical response as well as serum calcium. Adjust active vitamin D and calcium supplements per steps 4-6 if indicated.



The recommended NATPARA dose is the minimum dose required to prevent both hypocalcemia and hypercalciuria. No dose adjustment is recommended in patients with mild to moderate renal or hepatic impairment.

Study details: A 24-week, randomized, multinational, double-blind, placebo-controlled phase 3 trial evaluated the efficacy and safety of NATPARA in 124 adults with hypoparathyroidism after an optimization period of up to 16 weeks.¹

Please see Important Safety Information on last two pages.

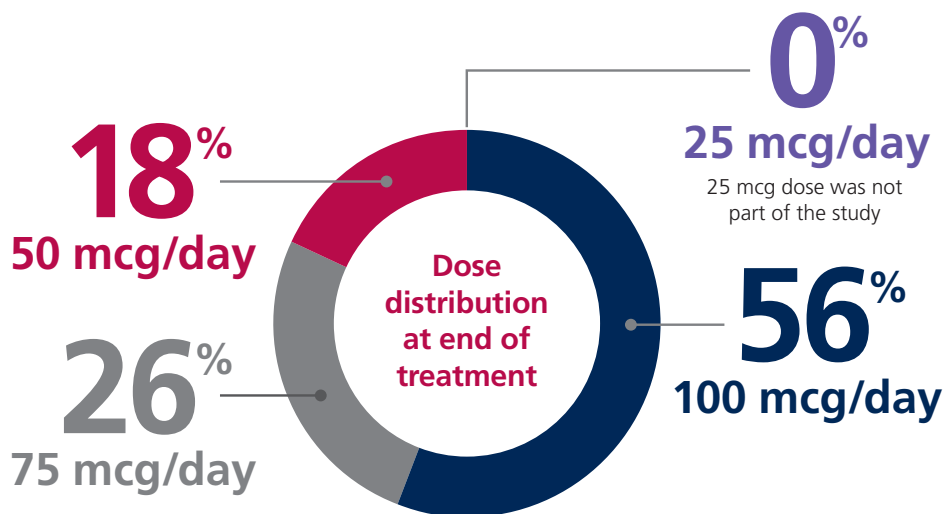
Please see [Full Prescribing Information](#), including Boxed Warning for potential risk of osteosarcoma.

The goal of NATPARA treatment is to achieve serum calcium within the lower half of the normal range.

MONITOR TREATMENT

Once a maintenance dose is achieved, regularly monitor per standard of care:

- Serum calcium
- 24-hour urinary calcium




After 24 weeks, the majority of NATPARA patients had been titrated up from the starting dose of 50 mcg*

*The maintenance dose should be the lowest dose that achieves a total serum calcium (albumin-corrected) within the lower half of the normal total serum calcium range (ie, approximately 8 and 9 mg/dL), without the need for active forms of vitamin D and with calcium supplementation sufficient to meet daily requirements.

The dose of NATPARA should be individualized based on total serum calcium (albumin-corrected) and 24-hour urinary calcium excretion.

For full dosage and administration instructions, please see the full Prescribing Information for NATPARA, including section 2.7: NATPARA Reconstitution and Administration Instructions.

Please see Important Safety Information on last two pages.
Please see [Full Prescribing Information](#), including Boxed Warning for potential risk of osteosarcoma.

 **Natpara**[®]
(parathyroid hormone)
for Injection
25 • 50 • 75 • 100 mcg per dose strength

Mixing and administering NATPARA®

Patients will receive injection training

- NATPARA is a self-administered, once-daily subcutaneous injection using a device called a Q-Cliq™ pen
- OnePath, Shire's product support service, will send a nurse educator to your patient's home to provide training on how to assemble the device and mix, administer, and store NATPARA
- Each assigned nurse educator will be available to assist patients during their first treatment cycle (first 28 days)

31G x 8 mm
BD Ultra-Fine™ Pen Needle



(Actual size)

Patients will be instructed on how to:	Patients should be advised:
Properly use the mixing device	To always follow the Instructions for Use
Properly use the Q-Cliq pen	Not to share their delivery device with other patients
Properly dispose of sterile 31G x 8 mm BD Ultra-Fine™ Pen Needles and alcohol swabs	To use a new Pen Needle for each injection

Indications and Usage¹

NATPARA® (parathyroid hormone) for Injection is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.

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.

Important Safety Information¹

WARNING: 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 adults 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.

For more information about the NATPARA REMS program, call 1-855-NATPARA or go to www.NATPARAREMS.com.



Natpara®
(parathyroid hormone)
for Injection

25 • 50 • 75 • 100 mcg per dose strength

Please see additional Important Safety Information on the next page.
Please see [Full Prescribing Information](#), including Boxed Warning for potential risk of osteosarcoma.

Important Safety Information¹ (continued)

Contraindications

NATPARA is contraindicated in patients with a known hypersensitivity to any component of NATPARA. Hypersensitivity reactions (e.g., anaphylaxis, angioedema, and urticaria) have occurred with NATPARA.

Warnings and Precautions

Hypercalcemia: Severe hypercalcemia has been reported with NATPARA. The risk is highest when starting or increasing the dose of NATPARA but can occur at any time. Monitor serum calcium and patients for signs and symptoms of hypercalcemia. Treat hypercalcemia per standard practice and consider holding and/or lowering the dose of NATPARA if severe hypercalcemia occurs.

Hypocalcemia: Severe hypocalcemia has been reported in patients taking NATPARA, including cases that resulted in seizures. The risk is highest with interruption or discontinuation of NATPARA treatment but can occur at any time. Monitor serum calcium and patients for signs and symptoms of hypocalcemia, and replace calcium and vitamin D if indicated in patients interrupting or discontinuing NATPARA to prevent severe hypocalcemia.

Digoxin Toxicity: Hypercalcemia increases the risk of digoxin toxicity. In patients using NATPARA concomitantly with digoxin, monitor serum calcium more frequently and increase monitoring when initiating or adjusting NATPARA dose.

Hypersensitivity: There have been reports of hypersensitivity reactions in patients taking NATPARA. Reactions included anaphylaxis, dyspnea, angioedema, urticaria, and rash. If signs or symptoms of a serious hypersensitivity reaction occur, discontinue treatment with NATPARA, treat hypersensitivity reaction according to the standard of care, and monitor until signs and symptoms resolve. Monitor for hypocalcemia if NATPARA is discontinued.

Adverse Reactions

The most common adverse reactions associated with NATPARA and occurring in greater than 10% of individuals were: paresthesia, hypocalcemia, headache, hypercalcemia, nausea, hypoaesthesia, diarrhea, vomiting, arthralgia, hypercalciuria and pain in extremity.

Drug Interactions

Alendronate: 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.

Use in Specific Populations

There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The safety and efficacy in pediatric patients have not been established.

Reference: 1. NATPARA [package insert]. Lexington, MA: Shire-NPS Pharmaceuticals, Inc.

Please see [Full Prescribing Information](#), including **Boxed Warning** for potential risk of osteosarcoma.

NATPARA® is a registered trademark of Shire-NPS Pharmaceuticals, Inc.

OnePath® is a registered trademark of Shire or its affiliates.

Q-Cliq™ is a trademark of Shire-NPS Pharmaceuticals, Inc. Ultra-Fine™ is a trademark of Becton-Dickinson.

©2019 Shire US Inc., Lexington, MA 02421. 1-800-828-2088. All rights reserved.

SHIRE and the Shire logo are trademarks or registered trademarks of Shire Pharmaceutical Holdings Ireland Limited or its affiliates. 545127 01/19

