January 21, 2020

Dear Healthcare Provider,

On behalf of Takeda, I am writing to update you about the status of NATPARA® (parathyroid hormone) for injection in the US. We have worked closely with the Food and Drug Administration (FDA) over the last several months on our proposed plan to bring NATPARA back to patients. Based on data generated from additional testing and feedback from the FDA, it is now clear that additional product modifications and testing will be required that will significantly impact our timelines. While we are continuing to work toward resupply as quickly as possible, I am disappointed to share that the additional testing and potential device modifications will likely cause more than a year's delay in bringing NATPARA back to US patients. We deeply regret this difficult news. Additional work is ongoing with the FDA, and we will continue to keep you informed as new information becomes available.

While we continue this critically important work, we are also committed to ensuring supply, through the Special Use Program, to patients previously prescribed NATPARA who are at extreme risk of life-threatening complications as a result of discontinuation of treatment. To date, 358 patients are receiving NATPARA at no cost as part of the Program, which was developed in collaboration with the FDA.

We understand that the Special Use Program is extremely limited and will not address the broader needs of patients who were previously prescribed NATPARA. As we have communicated previously, the Special Use Program requires that product usage be limited to a single dose per cartridge, instead of 14 doses per cartridge, to minimize the potential of particle formation caused by repeat punctures. This means that patients enrolled in the Special Use Program use one year's worth of cartridges each month. Because of this, we must limit the Program to patients who are at significant risk of life-threatening complications to ensure supply for the most high-risk patients.

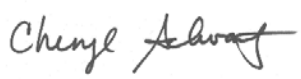
We know that this is not the news you were hoping to hear, and we recognize how difficult this interruption in therapy has been for you, your patients and their families. Our top priority, and our commitment to you all, is to continue to work with the FDA to identify all potential options for getting this critical medication back as quickly and as safely as we can.

We recognize that you also may have questions about members of the Takeda team with whom you have worked over the last few years. We want to assure you that we are committed to these valued team members. In the coming months, some of these employees may move to other parts of our business while we work to resolve this issue. However, we will continue to provide support to you and Special Use Program patients via a dedicated field medical and patient services team, and will redeploy a broader team as soon as the time of US resupply.

Shire-NPS Pharmaceuticals, Inc., part of the Takeda Group
300 Shire Way
Lexington, MA 02421
USA

If you have any questions, please do not hesitate to reach out to our medical information department at 1-800-828-2088.

Sincerely,



Cheryl Schwartz
Head of US Hematology & Rare Disease Business Unit

Indications and Usage

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 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.

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.

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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.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch** or call **1-800-FDA-1088**.

Please go to **https://www.shirecontent.com/PI/PDFs/Natpara_USA_ENG.pdf** **for the Full Prescribing Information and Medication Guide.**

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