Information Regarding the US NATPARA® (parathyroid hormone) for Injection Recall

The latest news about the US NATPARA Recall will be posted here as it becomes available. Takeda is committed to supply integrity, and we are working closely with the FDA to resolve the issue and resume supply as soon as possible.

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Please see Full Prescribing Information, including Boxed Warning for potential risk of osteosarcoma.

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S52147 09/19
Dear Healthcare Provider,

The purpose of this letter is to inform you of a temporary Special Use Program to obtain and use NATPARA (parathyroid hormone) for Injection as a result of the recent recall of NATPARA causing a shortage of available product.

In order to allow continued access of NATPARA, Takeda has worked with the FDA to develop a Special Use Program with the intent of allowing NATPARA to be accessed by those patients that are facing severe health consequences due to an inability to receive NATPARA.

As part of this program, in order to minimize the potential risk of adverse events, Takeda will supply NATPARA multiple-dose cartridge; however, patients must be counselled to use this cartridge for a SINGLE DOSE ONLY, puncturing each cartridge only one time. SEE DOSING and ADMINISTRATION section below for more information.

Obtaining Product: This Special Use Program allows physicians to submit a request to Takeda to explain the severe and/or life threatening medical situation facing the patient, and an adjudication committee will review the case, using criteria reviewed and approved by internal and external medical personnel and the FDA. The Special Use Program is intended to be a temporary program to aid in the supply of NATPARA to individual patients who are likely to face severe and/or life-threatening health consequences from interruption or discontinuation of NATPARA. The program does not and cannot guarantee access to drug to any individual or group of patients. HCPs who believe they have a patient meeting the criteria outlined below should contact Takeda at NatparaSpecialUseProgram@Takeda.com

Once approved through the Takeda adjudication process, which includes an external board certified endocrinologist, and upon order of the physician, product will be provided free of charge and shipped to the physician or, at the physician’s direction, to the patient based upon individual circumstances. Product dosage will be aligned as prescribed by the physician and enough NATPARA kits will be provided to allow for a SINGLE USE per cartridge. Takeda will provide a 28-day supply (14 kits containing 28 cartridges). A subsequent 28-day supply will be authorized at approximately day 21, pending confirmation of appropriate accounting of used cartridges returned by the patient, reaffirmation of continued patient needs by prescriber and review by the adjudication committee.

These unique administration instructions for use, including retention and collection of cartridge after one single dose (outlined below), must be reviewed in detail with the patient by the prescribing physician prior to the patient receiving product. In order to participate in this program, patients must agree to adhere to the below Dosing/Administration and Product Discard Instructions.

Dosing and Administration: Each NATPARA cartridge under the Special Use Program is intended for SINGLE USE ONLY; the used cartridge with remaining product is to be returned to Takeda as outlined below. Reconstitution and administration should follow the approved package labeling instructions except that each cartridge should only be used for a SINGLE DOSE. The Patient Consent
Product Discard Instructions: After reconstitution and administration of a single dose per NATPARA cartridge, the HCP must inform the patient that any remaining product should returned to Takeda, on a regular basis, utilizing the return instructions and shipping materials provided to the patient with each product delivery. Takeda will remind the patient of this requirement periodically and additional training will be offered as deemed necessary. Takeda will perform an accounting of retrieved product and report any deviation back to the Adjudication Committee.

Product Risk: Lots of NATPARA were recently recalled causing a shortage of available product. The recall was conducted due to the potential for rubber particulate from the rubber septum component of the NATPARA cartridge to enter the drug solution and clog the needle leading to underdosing. In such cases, there would be a risk of acute hypocalcemia when the patient/healthcare provider is unaware of receiving lower than required doses of NATPARA. In its most severe presentation, hypocalcemia may result in seizures, cardiac arrhythmias, altered mental status and cardiac arrest. There have been no post-marketing reports of clogged needles, sub-dosing or complication reports. During the approved 14-day NATPARA treatment period, the septum is punctured by a needle each day to obtain the daily dosage of NATPARA solution. When the septum is repeatedly punctured, it is possible that small rubber fragments may detach into the cartridge. Using each NATPARA cartridge for only a single dose is anticipated to eliminate this from occurring.

Reporting Adverse Events
Adverse reactions or quality problems experienced with the use of this product may be reported to the US FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax.

- Complete and submit the report Online: [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)
- Regular Mail or Fax: Download form [https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda](https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda) or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178 (1-800-332-0178)

Alternatively, adverse events can also be reported to Takeda by calling 1-800-828-2088

Medical Information
You may also contact our medical information department at 1-800-828-2088 if you have any questions about the information contained in this letter or the safe and effective use of NATPARA.

This letter is not intended as a complete description of the benefits and risks related to the use of NATPARA. Please refer to the enclosed Full Prescribing Information and Medication Guide. For additional information, please call Takeda at 1-800-828-2088 or visit www.natpara.com.

Sincerely,

Tom Koutsavlis, MD, FRCPC
Head, US Medical

NATPARA® is a registered trademark of Shire-NPS Pharmaceuticals, Inc., a Takeda company.
Please see Full Prescribing Information, including Boxed Warning for potential risk of osteosarcoma.
Takeda Announces NATPARA® Special Use Program in the US

Takeda has worked with the FDA to develop a Special Use Program for NATPARA®. The program is intended to support patients previously prescribed NATPARA who are facing life-threatening complications as a result of discontinuation of NATPARA. Through this program, healthcare providers will be able to request NATPARA for these extraordinary, life-threatening cases. It is anticipated that an extremely small number of patients prescribed NATPARA will qualify for this very limited program. Additional information for healthcare providers about the Special Use Program can be found here. Patients who have questions about their eligibility under the Special Use Program or about their individual treatment plans should consult with their healthcare providers.

We realize that while this program is an important first step, it will only help a very small number of patients. We recognize that many more patients are in need of NATPARA to control their hypoparathyroidism. Takeda continues to work with the FDA on both short- and long-term solutions to bring NATPARA back to the broader patient community, which remains our highest priority.

We are committed to the hypoparathyroidism community and the safe supply of NATPARA. We will continue to work urgently on this issue and keep patients and healthcare providers informed of our progress in resuming supply.

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.
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.

Please see Full Prescribing Information, including Boxed Warning for potential risk of osteosarcoma.
US Recall of NATPARA® (parathyroid hormone) for Injection

IMPORTANT INFORMATION REQUIRING ACTION

Dear Healthcare Provider,

The purpose of this letter is to inform you that Takeda has issued a US recall for all doses of NATPARA® (parathyroid hormone) for Injection (25 mcg, 50 mcg, 75 mcg, and 100 mcg). The recall is effective immediately. This recall is being conducted after discussions with the US Food and Drug Administration (FDA) and is due to a potential issue related to rubber particulates originating from the rubber septum of the NATPARA cartridge. During the 14-day NATPARA treatment period, the septum is punctured by a needle each day to obtain the daily dosage of medicine solution. When the septum is repeatedly punctured, it is possible that small rubber fragments may detach into the cartridge.

The recall includes all doses of NATPARA. It is important that healthcare providers immediately contact their patients to help ensure safe discontinuation of NATPARA treatment.

The safety profile of NATPARA remains consistent with the product label.

In light of this recall, we would like to remind you that abrupt discontinuation of NATPARA or dose interruption in patients can result in severe hypocalcemia as stipulated in the NATPARA Full Prescribing Information:

2.6 NATPARA 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, monitor for signs and symptoms of hypocalcemia and serum calcium levels.

5.4 Warnings and Precautions: Hypocalcemia

Severe hypocalcemia has been reported in patients taking NATPARA, including cases of hypocalcemia that resulted in seizures. The risk is highest when NATPARA is withheld, missed or abruptly discontinued, but can occur at any time. Monitor serum calcium and patients for signs and symptoms of hypocalcemia. Resume treatment with, or increase the dose of, an active form of vitamin D or calcium supplements or both if indicated in patients interrupting or discontinuing NATPARA to prevent severe hypocalcemia.

Therefore, as your patients discontinue NATPARA, it is very important to closely monitor serum calcium levels and observe for signs and symptoms of hypocalcemia in these patients while carefully titrating active vitamin D and supplemental calcium doses to maintain serum calcium levels within the lower half of the normal range (i.e., between 8 and 9 mg/dL). Please be aware that some patients may
require doses of oral active vitamin D and supplemental calcium that are higher than that which they required prior to starting NATPARA.

As with any interruption in NATPARA treatment, you should notify your patients of the significant risk of severe hypocalcemia when discontinuing NATPARA and the need for close follow-up and the importance of urgently contacting you if they experience signs or symptoms of hypocalcemia.

Please know that your patients will be notified directly through Takeda OnePath® patient services and advised to contact you for your medical recommendations.

Takeda is committed to supply integrity, and we are working closely with the FDA to resolve the issue in a timely manner and resume supply.

Reporting Adverse Events
Adverse reactions or quality problems experienced with the use of this product may be reported to the US FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax.

- Complete and submit the report online: https://www.accessdata.fda.gov/scripts/medwatch/index.cfm
- Regular Mail or Fax: Download form www.fda.gov/MedWatch/getforms.htm, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178
- Call 1-800-332-1088 to report by phone

Medical Information
You may also contact our medical information department at 1-800-828-2088 if you have any questions about the information contained in this letter or the safe and effective use of NATPARA.

This letter is not intended as a complete description of the benefits and risks related to the use of NATPARA. Please refer to the enclosed full Prescribing Information and Medication Guide. For additional information, please call Takeda at 1-800-828-2088 or visit www.natpara.com.

Please see accompanying Full Prescribing Information, Medication Guide, and Instructions for Use for NATPARA attached.

Sincerely,

Tom Koutsavlis, MD, FRCPC
Head, US Medical

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Enclosure: NATPARA Full Prescribing Information