**Takeda Provides NATPARA Regulatory Update**

[March 22, 2022] Takeda is providing a U.S. regulatory update for NATPARA® (parathyroid hormone) to inform that the Company has received a Complete Response Letter (CRL) from the U.S. Food and Drug Administration (FDA) in response to the Prior Approval Supplement (PAS) submitted in August 2021 to address the potential for rubber particulate formation that led to the U.S. NATPARA recall in September 2019.

The CRL indicates that the FDA has completed its review of the NATPARA PAS and determined that it cannot be approved in its present form. Takeda is evaluating the details of the CRL to determine next steps. In the meantime, we are deeply disappointed to inform the hypoparathyroidism community that NATPARA's commercial return in the U.S. is indefinitely delayed.

Importantly, because there are no U.S. FDA-approved treatment alternatives for chronic hypoparathyroidism patients, Takeda intends to provide patients who are enrolled in the NATPARA Special Use Program (SUP) with continued access to therapy free of charge, in accordance with regulatory oversight and under the discretion of the FDA, until a commercial product is available.

With the goal of limiting supply interruption for SUP patients, we continue to work on the separate supply challenges surrounding protein particle formation that we have described over the past year. Those challenges are unrelated to the PAS and the recall. It is important to underscore that all product released for patient use continues to meet Takeda's quality standards and the safety profile of NATPARA has not changed.

We understand and have tremendous empathy for how much the community has been impacted without NATPARA and are disheartened to share this update. We will continue to support this community and provide timely updates in the Takeda U.S. Newsroom at https://www.takeda.com/en-us/newsroom/natpara-updates/.

## What is NATPARA (parathyroid hormone) for Injection?

- NATPARA is a prescription parathyroid hormone used with calcium and vitamin D to control low blood calcium (hypocalcemia) in people with low parathyroid hormone blood levels (hypoparathyroidism).
- NATPARA is only for people who do not respond well to treatment with calcium and active forms of vitamin D alone, because it may increase the possible risk of bone cancer (osteosarcoma).
- NATPARA was not studied in people with hypoparathyroidism caused by calcium-sensing receptor mutations.

- NATPARA was not studied in people who get sudden hypoparathyroidism after surgery.
- It is not known if NATPARA is safe and effective for children 18 years of age and younger. NATPARA should not be used in children and young adults whose bones are still growing.

**IMPORTANT SAFETY INFORMATION**

**What is the most important information I should know about NATPARA?**

**Warning: Possible bone cancer (osteosarcoma).**

- During animal drug testing, NATPARA caused some rats to develop a bone cancer called osteosarcoma. It is not known if people who take NATPARA will have a higher chance of getting osteosarcoma. Tell your doctor right away if you have pain in any areas of your body that does not go away, or any new or unusual lumps or swelling under your skin that is tender to touch.

**NATPARA is only available through the NATPARA Risk Evaluation and Mitigation Strategy (REMS) Program.** The purpose of the NATPARA REMS program is to inform patients about the potential risk of osteosarcoma associated with the use of NATPARA. For more information about this REMS program, call 1-855-NATPARA (628-7272) or go to **www.NATPARAREMS.com**.

**NATPARA may cause other serious side effects, including:**

**High blood calcium (hypercalcemia)**

- NATPARA can cause some people to have a higher blood calcium level than normal.
  - Your doctor should check your blood calcium before you start and during your treatment with NATPARA.
  - Tell your doctor if you have nausea, vomiting, constipation, low energy, or muscle weakness. These may be signs that you have too much calcium in your blood.

**Low blood calcium (hypocalcemia)**

- People who stop using or miss a dose of NATPARA may have an increased risk of severe low blood calcium levels.
- Tell your doctor if you have tingling of your lips, tongue, fingers and feet, twitching of face muscles, cramping of feet and hands, seizures, depression, or have problems thinking or remembering.

Tell your doctor right away if you have any of these signs and symptoms of **high or low blood calcium** levels.

**Who should not use NATPARA?**

- **Do not use NATPARA** if you are allergic to parathyroid hormone or any of the ingredients in NATPARA.

**What should I tell my healthcare provider before using NATPARA?**

- **Before you start using NATPARA, tell your doctor about all of your medical conditions. Tell your doctor about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

**What are the possible side effects of NATPARA?**

- **NATPARA may cause serious side effects like allergic (hypersensitivity) reaction, including anaphylaxis**. Tell your healthcare provider or get emergency medical help right away if you have any of the following symptoms of an allergic reaction:
  - swelling of your face, lips, mouth, or tongue
  - breathing problems
  - fainting, dizziness, feeling lightheaded (low blood pressure)
  - fast heartbeat
  - itching
  - rash
  - hives

  **The most common side effects of NATPARA include:** tingling, tickling, or burning feeling of the skin, low or high blood calcium, headache, nausea, reduced sense of touch or sensation, diarrhea, vomiting, pain in joints, too much calcium in urine, and pain in limbs.

**These are not all the possible side effects of NATPARA. For more information, talk with your doctor.**

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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