September 15th, 2021

Dear Valued Patient,

You're receiving this update because you have previously been prescribed NATPARA® or you are part of our NATPARA® Special Use Program. Takeda is providing a regulatory filing update for NATPARA® (parathyroid hormone) for Injection in the US. The Company has submitted a Prior Approval Supplement (PAS) to the US Food & Drug Administration (FDA) as the next step in the Company's efforts to address the issue of rubber particulates originating from the rubber septum of the NATPARA cartridge that led to the US recall in September 2019. The submission proposes device component changes that include a new septum and new needle. US regulatory approval of the PAS is a critical step to bringing NATPARA back in the US, as the proposed changes are required to enable US patient use per the approved NATPARA labeling, which includes 14-day administration.

In April 2021, during a community call, our leadership team shared a few potential regulatory outcomes from FDA's review of this submission. Once FDA completes their review, the outcomes could include: 1) regulatory approval; 2) regulatory feedback that may require changes to our approach; or 3) significant regulatory feedback that may lead to starting the process over again. While Takeda is optimistic about the approach we have submitted to FDA, the timeline and outcome are still uncertain.

The next step in the regulatory process is for FDA to review our submission, which typically takes four to six (4-6) months after a PAS has been filed. This timeline could be extended should additional data or alternative proposals be required following regulatory discussions.

In addition, the supply and manufacturing issues that we described during the April call are separate from the issue that led to the US recall and remain complex. As we continue to work with urgency to address those issues, it is important to underscore that a potential FDA approval of the PAS is not the only variable that will determine how soon we can return NATPARA to the broader patient community. Our ability to provide a stable and consistent supply of NATPARA will also be a critical factor and remains an area of focus. During this process, it is important to underscore that patients enrolled in the Special Use Program (SUP) will continue to have access to NATPARA in the US through that Program.

We will plan to provide another update that includes the anticipated regulatory review timeline and a status update on the manufacturing/supply issues before the end of the 2021 calendar year. We understand how difficult the past two years have been for the community, and we remain committed to keeping you updated as we make progress in our efforts to bring NATPARA back.

As always, our OnePath® team is available to support you. Please reach out to a OnePath team member at 1-866-888-0660, Monday through Friday 8:30 a.m. to 8:00 p.m. ET.

Cheryl Schwartz
Head of U.S. Rare Disease Business Unit

Rick Ascroft
Senior Vice President, Patient Services & Managed Markets

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.

1. Your doctor should check your blood calcium before you start and during your treatment with NATPARA.
2. 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.

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.

Enclosure: NATPARA Full Prescribing Information