April Hypoparathyroidism Community Call Recap: Takeda Provides Updates Regarding Timeline to NATPARA US Resupply

On April 26, 2021, leaders from Takeda's US Medical Affairs, Research & Development (R&D) and US Commercial organizations hosted a video teleconference with the US hypoparathyroidism community. The purpose of the call was to respond to the patient community's requests for increased transparency and additional context following the March communication about NATPARA® (parathyroid hormone) for Injection and the latest estimated timeline to US resupply.

The call was led by **Cheryl Schwartz, Head of Takeda's US Rare Disease Business Unit**, and co-hosted by: **Tom Koutsavlis**, Head, US Medical Affairs and Chief Medical Officer for Takeda's US Business Unit; **Stefan Wildt**, Research & Development Chief Technology Officer and Head, Pharmaceutical Sciences; and **Anthony Frangie**, Head, US Lysosomal Storage Disorders and Endocrinology Franchise.

Opening Remarks – Cheryl Schwartz

Cheryl Schwartz opened the call by acknowledging that Takeda's March communication was a difficult message to deliver. She explained that the intent of that communication was to provide patients with the latest estimated timeline to NATPARA US resupply to enable patients and their healthcare providers to make the most informed healthcare decisions in the months ahead. She also apologized if the letter was perceived as insensitive.

Regarding the purpose of the call, Cheryl noted that Takeda has received feedback from a number of patients and other advocates across the hypoparathyroidism community requesting more clarity about the challenges impacting NATPARA's US resupply timeline. She also said that the Company has received questions about the cause of ongoing shortage notifications for some patients in the Special Use Program (or "SUP"), and whether the two issues are related.

Cheryl then introduced the Takeda call co-hosts and the topics they would be addressing.

SUP Program overview – Tom Koutsavlis

Tom Koutsavlis began with a review of the issues that led to the September 5, 2019 US recall for all doses of NATPARA (25-mcg, 50-mcg, 75-mcg and 100-mcg). Specifically, that the recall occurred after discussions with the FDA, due to the potential for rubber particulate from the rubber septum component part of the NATPARA cartridge to enter into the drug solution during the 14-day NATPARA treatment period. When the septum is repeatedly punctured, it is possible that small rubber fragments may detach into the cartridge. In response to frequent questions about the meaning of a "voluntary recall," Tom explained that a voluntary recall is a regulatory definition for initiating a recall **without requiring the FDA to file a legal action or court proceedings**. He clarified that most drug recalls in the US are labeled "voluntary" and that even though NATPARA was classified as a "voluntary recall," **it was still an action Takeda was required to take** under FDA's Code of Federal Regulations Title 21.

He then shared that the Special Use Program was put in place in direct response to healthcare providers who contacted Takeda with concerns that, for a very few, specific patients, abrupt discontinuation of NATPARA due to the recall would likely lead to life-threatening complications. Tom explained that when a product is the subject of a Class I recall, Federal law requires that the product be withdrawn from the market, and the manufacturer can no longer make the product available to patients. He then described how Takeda brought these healthcare provider concerns to the FDA, and worked quickly on an unprecedented program that, with US regulatory oversight, would give healthcare providers the ability to request NATPARA for extraordinary cases where patients were facing life-threatening consequences as a direct result of discontinuation of NATPARA. This is the NATPARA Special Use Program or "SUP".

Tom also walked through the SUP application process, which begins with a healthcare provider's initial assessment that a patient meets the Program criteria – including that the patient's risk for life-threatening complications **is a direct result of NATPARA discontinuation**. If the healthcare provider decides a patient meets the Program criteria, the provider would then submit an application to the adjudication committee with information evidencing the patient's life-threatening condition. Tom then explained that as part of the agreement with the FDA, a medical adjudication committee has been in place to assess all SUP applications to ensure they meet the strict requirements of the Program. The committee consists of both Takeda medical professionals and outside medical experts to ensure objectivity. He then underscored that the SUP was implemented with specific access and use restrictions to mitigate the risks associated with the recall.

In response to the frequently-asked question about why the SUP can't be extended to include all US patients who were prescribed NATPARA at the time of the US recall, Tom shared that NATPARA must be administered as single use (one dose per cartridge) due to the issue with components of the current device and the risk of rubber particulates being pushed into the medication vial if the stopper is punctured multiple times (i.e., the reason for the US recall). He explained that due to the single-use requirements, the SUP program, while only includes ~430 patients, requires **TWICE as much** supply of NATPARA as the entire NATPARA patient population required prior to the recall, because patients who were previously using a single cartridge fourteen (14) times are now only able to use a single cartridge once.

Status of NATPARA Device Remediation Efforts – Stefan Wildt

Stefan Wildt began by sharing the scope of the extended team that's been focused on addressing the issues that led to the US recall. He underscored the Takeda's ongoing commitment, including that the Company has dedicated significant resources across the organization to find a way to get NATPARA back to US patients.

Stefan then walked through the Company's efforts to fix the NATPARA device components, and explained that those efforts first included a number of potential shorter-term approaches. He listed some of those approaches, including the possibility of fewer than 14 punctures per medication cartridge, testing the needle that twists through the rubber septum, and examining the rotation during needle insertion, among other aspects of the device. He spoke about the time associated with testing these types of approaches, and said it can involve: designing studies that will appropriately address

regulatory questions; conducting the studies; generating and analyzing sufficient data and compiling the reports; and drawing conclusions. And, he shared that when necessary, the timeline also may include redesigning the studies and going back to the first step.

Stefan explained that when the early tests failed to identify a relatively short-term fix to the device, the team had to pivot to work on more complex, robust and reliable solutions. He expressed that it was a disappointing time for the large team working on solving the device issues, and said it was at that time that Takeda communicated a delay of at least one year in January 2020.

In terms of where things stand as of April 2021, Stefan shared that, after a significant amount of testing, **Takeda has reached an approach that involves changing two components of the device: a new rubber septum and a new needle.** Stefan said that **the latest estimate for Takeda to submit the data to FDA is by late summer.** Given that various prior approaches explored by Takeda were not viable, it is important to clarify here that none of the previous approaches tested by Takeda were submitted to FDA for formal review. However, since the US recall began, Takeda has been in frequent contact with FDA. The Agency has been responsive and supportive of Takeda's efforts to date.

Stefan explained that the typical regulatory review timeline for this kind of submission can be 4-6 months. He added that there are a few potential regulatory outcomes, such as 1) regulatory approval, 2) regulatory feedback that may have required minor or moderate changes to our approach, or 3) significant regulatory feedback that may lead to starting the process all over again. So, while he shared that Takeda is optimistic about having a potential solution, the timeline and outcome are, unfortunately, still far from certain. The best case, he said, would put an approval of the submission, a fix of the device issue, and return to the US market at about 10-12 months from now.

Recent Special Use Program Supply Challenges – Stefan Wildt

Stefan Wildt then introduced an emerging issue that is separate from the rubber particulate issue. He said that this separate issue has had an impact on SUP supply as well as the ability to provide consistent, reliable and stable supply in the future. Stefan then explained that NATPARA is produced in "batches," which are based on dosage strengths, for example the 25 mcg, 50 mcg, 75 mcg and 100 mcg doses. He said that during and after the manufacturing process, every batch must meet pre-defined, rigorous manufacturing and quality standards that have been agreed upon with FDA. Stefan explained that if a batch does not meet those rigorous standards for any reason, it cannot be released for patient use and is destroyed.

Stefan then moved on to describe the visual inspection of the product. For NATPARA, the regulatory release requirements include that the drug product solution is clear and essentially free from particles. The new issue that is impacting SUP supply for specific doses of NATPARA, he said, is due to a higher percentage of batches that have not met the visual inspection requirements.

Explaining that the manufacturing process for NATPARA is particularly complex because it is a molecule that is extremely sensitive to manufacturing stresses, which can result in some product lots not meeting the quality standards established with the FDA, he shared the steps that Takeda is actively working to understand: 1) why there has been an increase in the number of batches that do not meet the required

visual release criteria and why that's happening at a much higher rate than ever before, and 2) why the manufacturing stress appears to be impacting the higher concentration doses (e.g., the 100-mcg dose) at higher rates than the other doses.

Stefan went on to describe that the batches that have failed visual inspection have included "clumping" or "cloudiness" that shows the presence of protein particles. If protein particles are observed in the drug solution, he said, the product may not meet the release specifications. He then underscored that 1) if product does not meet the regulated specifications for release, Takeda cannot and would not supply it to patients; and 2) that **all batches that have been released for any patient use HAVE MET quality standards agreed upon with the FDA** and are considered safe for use.

In terms of the recent supply interruptions within the SUP, Stefan noted that Takeda has already communicated the impact to the 100-mcg dose, and that the Company is watching other doses closely while continuing to work to investigate and then address the issue. In closing, he explained that beyond creating challenges to SUP supply, these issues are also contributing to the latest projection that NATPARA's resupply timeline in the US is at least 10-12 months out from now.

Following a Q&A session moderated by **Anthony Frangie**, Cheryl closed the call, emphasizing that the extended team understands what NATPARA means to patients and their families. She reiterated Takeda's commitment to the hypoparathyroidism community, to increased transparency moving forward and to continuing the work to fix the issues that have come up with the goal of bringing NATPARA back.

A recording of the WebEx call – including the full Q&A session – will be posted to https://www.natpara.com/recall.html in the coming weeks.

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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