March 31, 2021

Dear Healthcare Provider,

We are writing to provide you with information on the status of the NATPARA recall in the U.S. and a supply update for patients receiving NATPARA® (parathyroid hormone) for Injection through the Special Use Program (SUP).

While we have made progress on the original issue that led to the U.S. recall, which was the issue of rubber particulates originating from the rubber septum of the NATPARA cartridge, we have not yet reached a resolution. We continue to face complex challenges in bringing NATPARA back to the broader patient community in the U.S.

As we have communicated previously, we continue to monitor all doses of NATPARA within the Special Use Program based on the extraordinary supply demands of the Program. As part of our rigorous quality and manufacturing processes, we have experienced a delay that has affected the manufacturing and release of NATPARA 100-mcg. This is separate from the issue of rubber particulates originating from the rubber septum of the NATPARA cartridge that led to the U.S. recall in September 2019.

The manufacturing delay that is currently affecting NATPARA 100-mcg within the SUP has further impacted our timelines, and at this time we do not expect a return to market before March 31, 2022. Patients who are enrolled in the SUP continue to have access to therapy, and we will keep the community informed of relevant updates as we progress. We regret that we are anticipating an interruption in supply of the 100-mcg strength and we are working with urgency to maintain supply continuity for all SUP patients.

Reporting Adverse Events
Healthcare providers and patients are encouraged to report adverse events in patients taking NATPARA to Takeda at 1-800-828-2088. You are encouraged to report negative side effects of prescription drugs to the U.S. Food & Drug Administration (FDA). Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Medical Information
You may also contact our medical information department at 1-877-TAKEDA-7 (1-877-825-3327) if you have any questions about the information contained in this message 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 1-877-TAKEDA-7 (1-877-825-3327) or visit www.natpara.com.

We realize this update may be difficult for those who have been eagerly awaiting information about our anticipated timelines for bringing back NATPARA, and we are disappointed there is not better news to share.

Sincerely,

Tom Koutsavlis
Head, US Medical

Enclosure: NATPARA Full Prescribing Information

US-NAT-0391v1.0 3/21

Time-Sensitive Information Regarding Your Patients Receiving NATPARA 75-mcg or NATPARA 100-mcg

February 5, 2021

Dear Healthcare Provider,

The purpose of this letter is to inform you of a potential short-term supply interruption for some patients receiving NATPARA 75-mcg or NATPARA 100-mcg through the Special Use Program (SUP). An inventory processing delay, compounded by a severe winter storm during the week of February 1, 2021, has impacted the NATPARA® (parathyroid hormone) shipping schedule. There are some patients who could experience a brief supply interruption of NATPARA 75-mcg or NATPARA 100-mcg between now and the end of the second week of February. It is therefore with a sense of urgency that we are contacting you at this time. Pending any additional unanticipated delays, we have already rescheduled shipments and expect the supply interruption to be fully addressed by February 11.

This short-term supply interruption is NOT the result of any quality or manufacturing issues. This situation is not impacting NATPARA 50-mcg or NATPARA 25-mcg. However, based on the supply demands of the Special Use Program, we continue to closely monitor all NATPARA doses. We are committed to supply continuity and will provide a general update on all NATPARA doses by the end of March 2021.

Takeda's OnePath Patient Support Managers are reaching out to all impacted patients directly to emphasize the urgency of contacting their prescribing physicians to discuss the best treatment approach. OnePath is also contacting physicians whose patients may require an alternate treatment plan. Based on your independent medical judgement, if your revised treatment plan requires a new prescription, please contact Takeda OnePath at 866-888-0660 as soon as possible for your patient to receive a 7-day supply of the back-up prescription. After resolution of the supply interruption, a OnePath Patient Support Manager will follow up with you to confirm that we should resume shipments according to the patient's current prescription.

If based on previous communication of a potential for supply interruption, you had already submitted a prescription form modifying the dose for a patient currently receiving NATPARA 75-mcg or NATPARA 100-mcg, there's nothing more to do at this time. This updated prescription form will be processed in advance of the patient's supply interruption. A Takeda OnePath® Patient Support Manager will follow up with the patient and answer questions related to supply and the SUP.

For any of your patients who may be affected by a NATPARA dose interruption, please review Section 2.6 (NATPARA Dose Interruption or Discontinuation) and Section 5.4 (Warnings and Precautions: Hypocalcemia) in the attached NATPARA Full Prescribing Information. It is very important to closely monitor serum calcium levels and observe for signs and symptoms of hypocalcemia in these patients while carefully adjusting active vitamin D and supplemental calcium doses. Some patients may require higher doses of active vitamin D and supplemental calcium than doses required prior to starting NATPARA. Additional guidance regarding NATPARA treatment interruption was previously issued in a joint statement by the Endocrine Society and American Society for Bone and Mineral Research (ASBMR) at the following URL: https://endocrinenews.endocrine.org/endocrine-society-asbmr-issue-joint-statement-on-natpara-recall/.

Compliance with Special Use Program Terms & Conditions
It is important to remind SUP-enrolled patients that each NATPARA cartridge under the Special Use Program (single dose use) is intended for one use only, and that used cartridges with remaining product are to be returned to Takeda in accordance with the Special Use Program (single dose use) instructions. Non-compliance with the rules under the Special Use Program (single dose use) could result in termination of the patient's ability to receive NATPARA product through the program.

Reporting Adverse Events
Healthcare providers and patients are encouraged to report adverse events in patients taking NATPARA to Takeda at 1-800-828-2088. You are encouraged to report negative side effects of prescription drugs to the U.S. Food & Drug Administration (FDA). Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Medical Information
You may also contact our medical information department at 1-877-TAKEDA-7 (1-877-825-3327) 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 1-877-TAKEDA-7 (1-877-825-3327) or visit www.natpara.com.

We recognize the important medical need that NATPARA fills for your hypoparathyroidism patients. While we focus on ensuring supply continuity for SUP-enrolled patients, we continue to prioritize the goal of safely bringing NATPARA back to the broader patient community with U.S. Regulatory Authority oversight.

Sincerely,

Tom Koutsavlis
Head, US Medical

Enclosure: NATPARA Full Prescribing Information

US-NAT-0365v1.0 2/21

December 22, 2020

Dear Healthcare Provider,

We are writing to share a supply-status update to the information we provided during the week of December 14, regarding the potential for near-term supply interruptions of NATPARA® (parathyroid hormone) for Injection that may impact U.S. patients receiving NATPARA through the Special Use Program.

Since that supply update, the manufacturing disruption impacting the availability of NATPARA 100-mcg and NATPARA 75-mcg has now been mitigated. This means that we are no longer expecting near-term supply interruptions for any NATPARA dose for patients receiving NATPARA through the Special Use Program.

If you have submitted an updated prescription form modifying the dose for a patient currently receiving NATPARA 100-mcg or NATPARA 75-mcg through the SUP, thank you for your diligence in preparing for the potential supply interruption. Since the updated prescription was only to be actioned in the event of an actual stockout of either of these strengths, your patient will continue to receive their current dosing prescription of NATPARA according to their regular shipment schedule. Revised prescriptions that were submitted in preparation for potential near-term supply interruptions will be kept on file in the event of a future supply interruption. If you would like to make any changes to your patient's current prescription, please contact OnePath® at 866-888-0660, Monday through Friday 8:30 AM – 8:00 PM ET, to be connected to the pharmacy dispensing the medication for this program.

Takeda OnePath® Patient Support Managers plan to reach out to patients receiving either NATPARA 100-mcg or NATPARA 75-mcg in the coming days to provide the update that we are no longer expecting near-term supply interruptions for NATPARA and to answer questions related to the patient's shipment schedule or the Special Use Program.

We recognize that we have been communicating about supply frequently since October 2020, and we are doing that to ensure that you and your patient have time to discuss treatment plans in the event of actual NATPARA supply interruptions. This is especially important because any potential interruption or reduction in the daily dose of NATPARA can cause a sharp decrease in blood calcium levels (severe hypocalcemia) which can be dangerous. We appreciate your patience during the past few months as we worked to maintain supply continuity.

At this time, we do not anticipate near-term supply interruptions for any NATPARA dose. However, we are closely monitoring all NATPARA doses based on the supply demands of the Special Use Program. We are committed to supply continuity and will provide another update on all NATPARA doses by March 2021.

Compliance with Special Use Program Terms & Conditions
It is important to remind SUP-enrolled patients that each NATPARA cartridge under the Special Use Program (single dose use) is intended for one use only, and that used cartridges with remaining product are to be returned to Takeda in accordance with the Special Use Program (single dose use) instructions. Non-compliance with the rules under the Special Use Program (single dose use) could result in termination of the patient's ability to receive NATPARA product through the program.

Reporting Adverse Events
Healthcare providers and patients are encouraged to report adverse events in patients taking NATPARA to Takeda at 1-800-828-2088. You are encouraged to report negative side effects of prescription drugs to the U.S. Food & Drug Administration (FDA). Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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

We appreciate your patience over the past few months as we worked to maintain supply continuity.

Sincerely,

Tom Koutsavlis
Head, US Medical

Enclosures: NATPARA Full Prescribing Information

US-NAT-0357v1.0 12/20

December 16, 2020

Dear Healthcare Provider,

We are writing to provide the latest update regarding the potential for a near-term supply interruption of NATPARA® (parathyroid hormone) for Injection that may impact U.S. patients receiving NATPARA 100-mcg through the Special Use Program (SUP). Since our last communication during the week of November 16, we are notifying you that we are now preparing for a potential near-term supply interruption of NATPARA 75-mcg, in addition to the anticipated supply interruption of NATPARA 100-mcg.

It is important to note that the manufacturing disruptions that are impacting NATPARA supply are fluid. We are working with urgency, and with U.S. regulatory oversight, to address these issues and maintain supply continuity for all NATPARA doses. We could have additional information available as soon as the week of December 21, 2020. In the meantime, we want to ensure that you and your patients receiving NATPARA 100-mcg or NATPARA 75-mcg through the Special Use Program are prepared in the event of near-term supply interruptions for these NATPARA doses.

Please see the following time-sensitive information should you wish to consider alternative treatment plans for patients receiving the 100-mcg dose or the 75-mcg dose of NATPARA. Supply status updates for all other NATPARA doses are also included in this communication.

Time-Sensitive Information Regarding Patients Receiving NATPARA 100-mcg or NATPARA 75-mcg

As we communicated in November, we have been monitoring supply of NATPARA to prepare for potential supply interruptions. We are working with urgency and with U.S. regulatory oversight to resolve the manufacturing issues that are impacting supply. Based on our current assessments, we are anticipating supply interruptions for NATPARA 100-mcg as early as **January 2, 2021**, as well as for NATPARA 75-mcg, as early as **mid-January.**

Takeda cannot make dosing recommendations beyond those reflected in the NATPARA Full Prescribing Information. However, if in your best independent clinical judgement, you would like to change the current NATPARA dose of patients currently receiving the 100-mcg or the 75-mcg dose of NATPARA, please complete and return the enclosed prescription form to expedite the process of updating your patient's NATPARA dose and avoid a disruption in treatment in the event of a supply interruption.

If you have already submitted a prescription form that modifies the dose for a patient currently receiving NATPARA 100-mcg through the SUP, **and the modified dose does not include the use of NATPARA 75-mcg**, there's nothing more that you need to do. In preparation for the anticipated January 2, 2021 supply interruption of the NATPARA 100-mcg dose, the updated prescription form that you've submitted will be processed in advance of the patient's supply interruption. **However, if you have provided a modified dose for a patient currently receiving NATPARA 100-mcg that includes the use of NATPARA 75-mcg, you will need to submit an updated prescription form that does not include the 75-mcg or 100-mcg dosage strengths in order to avoid a disruption to your patient's therapy in the event of a supply interruption.** A Takeda OnePath® Patient Support Manager will follow up with your patient and can answer questions related to supply and the Special Use Program.

For patients currently receiving NATPARA 75-mcg, **or if a modified prescription had been submitted and included NATPARA 75-mcg for a patient currently receiving NATPARA 100-mcg**, please complete and submit the enclosed form. Any changes that you make using the enclosed form will only be processed if a supply disruption occurs. If you need to make an immediate prescription change, please contact OnePath® at 866-888-0660, Monday through Friday 8:30 AM – 8:00 PM ET, to be connected to the pharmacy dispensing the medication for this program.

****Please note that if we do not receive an updated prescription form for any patient currently receiving NATPARA 100-mcg or NATPARA 75-mcg, we will be unable to ship NATPARA to that patient should a supply interruption occur, as anticipated. For patients receiving NATPARA 100-mcg, we would need to receive an updated prescription form by December 22, 2020. For patients receiving NATPARA 75-mcg, we would need to receive an updated prescription form by January 8, 2021.**

For any of your patients who may be affected by a NATPARA dose interruption, please review Section 2.6 (NATPARA Dose Interruption or Discontinuation) and Section 5.4 (Warnings and Precautions: Hypocalcemia) in the enclosed NATPARA Full Prescribing Information. It is very important to closely monitor serum calcium levels and observe for signs and symptoms of hypocalcemia in these patients while carefully adjusting active vitamin D and

supplemental calcium doses. Some patients may require higher doses of active vitamin D and supplemental calcium than doses required prior to starting NATPARA. Additional guidance regarding NATPARA treatment interruption was previously issued in a joint statement by the Endocrine Society and the American Society for Bone and Mineral Research (ASBMR) at the following URL: https://endocrinenews.endocrine.org/endocrine-society-asbmr-issue-joint-statement-on-natpara-recall/.

Update Regarding NATPARA 25-mcg and 50-mcg:
At this time, we do **not** expect SUP-enrolled patients who are receiving **NATPARA 25-mcg** or **NATPARA 50-mcg** to be impacted by near-term supply interruptions. However, we are closely monitoring all NATPARA doses based on the supply demands of the Special Use Program. We are committed to supply continuity and will provide another update on all NATPARA doses by mid-January. We have communicated this information to patients who are receiving NATPARA through the Special Use Program, and we have emphasized to patients receiving NATPARA 25-mcg or NATPARA 50-mcg that there is nothing they need to do at this time.

Compliance with Special Use Program Terms & Conditions
It is important to remind SUP-enrolled patients that each NATPARA cartridge under the Special Use Program (single dose use) is intended for one use only, and that used cartridges with remaining product are to be returned to Takeda in accordance with the Special Use Program (single dose use) instructions. Non-compliance with the rules under the Special Use Program (single dose use) could result in termination of the patient's ability to receive NATPARA product through the program.

Reporting Adverse Events
Heath care providers and patients are encouraged to report adverse events in patients taking NATPARA to Takeda at 1-800-828-2088. You are encouraged to report negative side effects of prescription drugs to the U.S. Food & Drug Administration (FDA). Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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

As we have communicated previously, this is a fluid situation and we continue to work with urgency, and with US regulatory authority oversight, to maintain supply continuity for patients receiving NATPARA through the Special Use Program. We could have updated information regarding NATPARA 100-mcg and NATPARA 75-mcg as soon as the week of December 21, 2020. We appreciate your patience as we work to address these issues.

Sincerely,

Tom Koutsavlis
Head, US Medical

Enclosures: NATPARA Full Prescribing Information
Special Use Program Updated Prescription Form

US-NAT-0350v1.0 12/20

November 16, 2020

Dear Healthcare Provider,

The purpose of this letter is to provide an update on the information we provided in October 2020 regarding the potential for a near-term supply interruption of NATPARA® (parathyroid hormone) for Injection that may impact U.S. patients receiving NATPARA 100-mcg through the Special Use Program (SUP). We are also notifying you that we are now anticipating a near-term supply interruption of NATPARA 25-mcg, as well.

Please see the following time-sensitive information should you wish to consider alternative treatment plans for patients receiving those doses of NATPARA. Supply status updates for all other NATPARA doses are also included in this letter.

Time-Sensitive Information Regarding Patients Receiving NATPARA 25-mcg or NATPARA 100-mcg

As we communicated in October, we have been monitoring supply of NATPARA to prepare for potential supply interruptions. Based on our current assessments, we are anticipating supply interruptions for NATPARA 25-mcg, as early as **December 8, 2020**, as well as NATPARA 100-mcg as early as **January 2, 2021.**

Takeda cannot make dosing recommendations beyond those reflected in the NATPARA Full Prescribing Information. However, if in your best independent clinical judgement, you would like to have a contingency plan in place that includes modifying the patient's current dose of NATPARA, please complete and return the enclosed prescription form. **Any changes to your patient's NATPARA dose, as indicated on this form, will only be processed if a supply disruption occurs**. **If you have already completed a new prescription form and faxed it to us, there is nothing more you need to do.** If you need to make an immediate prescription change, please contact OnePath® at 866-888-0660, Monday through Friday 8:30 AM – 8:00 PM ET, to be connected to the pharmacy dispensing the medication for this program.

For any of your patients who may be affected by a NATPARA dose interruption, please review Section 2.6 (NATPARA Dose Interruption or Discontinuation) and Section 5.4 (Warnings and Precautions: Hypocalcemia) in the attached NATPARA Full Prescribing Information. It is very important to closely monitor serum calcium levels and observe for signs and symptoms of hypocalcemia in these patients while carefully adjusting active vitamin D and supplemental calcium doses. Some patients may require higher doses of active vitamin D and supplemental calcium than doses required prior to starting NATPARA. Additional guidance regarding NATPARA treatment interruption was previously issued in a joint statement by the Endocrine Society and the American Society for Bone and Mineral Research (ASBMR) at the following URL: https://endocrinenews.endocrine.org/endocrine-society-asbmr-issue-joint-statement-on-natpara-recall/.

Update Regarding NATPARA 50-mcg and 75-mcg:
At this time, we do **not** expect SUP-enrolled patients who are receiving **NATPARA 50-mcg** or **NATPARA 75-mcg** to be impacted by supply interruptions before the end of 2020. However, we are closely monitoring these NATPARA doses (50-mcg and 75-mcg). We are committed to supply continuity and will provide another update on all NATPARA doses by mid-December. We have communicated this information to patients who are receiving NATPARA through the

Special Use Program, and we have emphasized to patients receiving NATPARA 50-mcg or NATPARA 75-mcg that there is nothing they need to do at this time.

Compliance with Special Use Program Terms & Conditions
It is important to remind SUP-enrolled patients that each NATPARA cartridge under the Special Use Program (single dose use) is intended for one use only, and that used cartridges with remaining product are to be returned to Takeda in accordance with the Special Use Program (single dose use) instructions. Non-compliance with the rules under the Special Use Program (single dose use) could result in termination of the patient's ability to receive NATPARA product through the program.

Reporting Adverse Events
Heath care providers and patients are encouraged to report adverse events in patients taking NATPARA to Takeda at 1-800-828-2088. You are encouraged to report negative side effects of prescription drugs to the U.S. Food & Drug Administration (FDA). Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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.

We recognize the important medical need that NATPARA fills for your hypoparathyroidism patients. While we focus on mitigating these supply interruptions for SUP-enrolled patients, we continue to prioritize the goal of safely bringing NATPARA back to the broader patient community with U.S. Regulatory Authority oversight.

Sincerely,

Tom Koutsavlis
Head, US Medical

Enclosures: NATPARA Full Prescribing Information
Special Use Program Updated Prescription Form

US-NAT-0159v1.0 11/20

October 20, 2020

Dear Healthcare Provider,

The purpose of this letter is to provide an informational update about the potential for a near-term supply interruption of NATPARA® (parathyroid hormone) for Injection that may impact U.S. patients receiving NATPARA 100-mcg through the Special Use Program (SUP). Takeda is notifying SUP-enrolled patients and their healthcare providers of the following time-sensitive actions. If none of your patients are receiving NATPARA 100-mcg through the NATPARA SUP, there is nothing you need to do at this time. Supply status updates for all other NATPARA doses are also included in this letter.

Time-Sensitive Information Regarding Patients Receiving NATPARA 100-mcg

Supply interruption of NATPARA 100-mcg is expected to occur as early as **November 21, 2020.** We are alerting healthcare providers and SUP-enrolled patients who are receiving NATPARA 100-mcg in the event that healthcare providers need to evaluate alternate treatment plans in anticipation of this expected supply interruption. A member of Takeda's OnePath Patient Services team will directly notify impacted patient(s) and advise them to contact their prescribing physician to assess what treatment plan adjustments may be required due to the expected supply interruption of the NATPARA 100-mcg dose.

Ensuring patient safety and supply continuity for patients with hypoparathyroidism are our highest priorities. Available product inventory has been impacted by unexpected manufacturing disruptions that are separate from the issue of rubber particulates originating from the rubber septum of the NATPARA cartridge. We are working with urgency to resolve the manufacturing issues that are affecting the availability of NATPARA 100-mcg. At the same time, we are working on possible mitigation options for impacted patients with U.S. Regulatory Authority (U.S. Food & Drug Administration or "FDA") oversight and will notify healthcare providers of any future approved options for alternate treatment plans.

For any patients who may be affected by a NATPARA dose interruption, we are emphasizing that the patient's prescribing physician should review Section 2.6 (NATPARA Dose Interruption or Discontinuation) and Section 5.4 (Warnings and Precautions: Hypocalcemia) in the attached NATPARA Full Prescribing Information. It is very important to closely monitor serum calcium levels and observe for signs and symptoms of hypocalcemia in these patients while carefully adjusting active vitamin D and supplemental calcium doses. Some patients may require higher doses of active vitamin D and supplemental calcium than doses required prior to starting NATPARA. Additional guidance regarding NATPARA treatment interruption was previously issued in a joint statement by the Endocrine Society and the American Society for Bone and Mineral Research (ASBMR) at the following URL: https://endocrinenews.endocrine.org/endocrine-society-asbmr-issue-joint-statement-on-natpara-recall/.

Update Regarding Patients Receiving NATPARA 25-mcg, 50-mcg or 75-mcg:

At this time, we do **not** expect SUP-enrolled patients who are receiving **NATPARA 25-mcg**, **NATPARA 50-mcg** or **NATPARA 75-mcg** to be impacted by the supply interruptions. However, we are closely monitoring the remaining NATPARA doses (25-mcg, 50-mcg and 75-mcg). We are committed to supply continuity and will provide an update on all NATPARA doses by November 16, 2020. We have communicated this information to patients who are receiving NATPARA through the Special Use Program, and we have emphasized to patients receiving NATPARA 25-mcg, NATPARA 50-mcg or NATPARA 75-mcg that there is nothing that they need to do at this time.

Compliance with Special Use Program Terms & Conditions

It is important to remind SUP-enrolled patients that each NATPARA cartridge under the Special Use Program (single dose use) is intended for one use only, and that used cartridges with remaining product are to be returned to Takeda in accordance with the Special Use Program (single dose use) instructions. Non-compliance with the rules under the Special Use Program (single dose use) could result in termination of the patient's ability to receive NATPARA product through the program.

Reporting Adverse Events
Healthcare providers and patients are encouraged to report adverse events in patients taking NATPARA to Takeda at 1-800-828-2088. You are encouraged to report negative side effects of prescription drugs to the U.S. Food & Drug Administration (FDA). Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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.

We recognize the important medical need that NATPARA fills for your hypoparathyroidism patients. While we focus on mitigating these supply interruptions for SUP-enrolled patients, we continue to prioritize the goal of safely bringing NATPARA back to the broader patient community with U.S. Regulatory Authority oversight.

Sincerely,

Tom Koutsavlis
Head, US Medical

Enclosure: NATPARA Full Prescribing Information

US-NAT-0140v1.0 10/20

September 24, 2019

Subject: IMPORTANT INFORMATION REGARDING NEW PROGRAM FOR OBTAINING AND USING NATPARA® (parathyroid hormone) for injection

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

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

Form will further detail this requirement directly to the patient and additional training will be offered for dosing and administration, as well as cartridge return, as requested by the Patient or HCP.

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
- **Regular Mail or Fax**: Download form 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

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

S52114 09/19

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

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

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.

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.

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.