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, Medication Guide, and Instructions for Use for NATPARA.

NATPARA® is a registered trademark of Shire-NPS Pharmaceuticals, Inc., a Takeda Company.

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US-NAT-0536v1.0 03/22
March 23, 2022

Dear Valued Patient,

You’re receiving this update because you have previously been prescribed NATPARA® (parathyroid hormone) for Injection or you are part of our NATPARA® Special Use Program (SUP). 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 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. Our Takeda OnePath® Patient Support Managers will continue to work with SUP patients to ensure they have access to their prescribed NATPARA treatment.

We understand and have tremendous empathy for how much the community has been impacted without NATPARA and are disheartened to share this update. Takeda leaders will host a video teleconference with the US hypoparathyroidism community to provide more context regarding this communication in the coming weeks. Please watch for more information about that upcoming event in the NATPARA Updates section of our Takeda US Newsroom at https://www.takeda.com/en-us/newsroom/natpara-updates/. Information should be posted before the end of March. We will also share the information with the HypoPARAthyroidism Association and HypoPara Support & Advocacy.

Cheryl Schwartz
Senior Vice President and Business Unit Head
US Rare Disease Business Unit

Richard C. Ascroft, RPh, JD
Senior Vice President
Patient and Market Access
US Business Unit
**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.
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- 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.

**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.

Enclosure: NATPARA Full Prescribing Information
December 20th, 2021

Dear Valued Patient,

You’re receiving this update because you have previously been prescribed NATPARA® (parathyroid hormone) for Injection or you are part of our NATPARA® Special Use Program (SUP). On behalf of Takeda, we would like to provide you with a year-end update.

FDA has acknowledged receipt of the Prior Approval Supplement (PAS) submission announced in September 2021. The NATPARA PAS submission proposes device component changes that include a new septum and new needle. These proposed changes are intended to address the issue of rubber particulates originating from the rubber septum of the NATPARA cartridge that led to the US recall in 2019.

FDA has communicated to Takeda that this PAS submission is associated with a six-month review timeline. Once the FDA completes their review, there are two potential regulatory outcomes of FDA’s review: 1) FDA approval of the PAS, or 2) regulatory feedback that may require significant changes to our proposed approach, or lead to a revised approach. If the FDA requests additional data or alternative proposals during or at the end of the review process, a new submission will be required, and the review/approval timelines will be extended.

While the NATPARA PAS submission represents an important step to address the original issue that led to the US recall, the manufacturing and supply issues that the Company has previously shared will also impact the timeline for bringing NATPARA back in the US. At this time, those issues remain complex.

Given the serious risks associated with abrupt discontinuation of NATPARA, the Company would not bring NATPARA back to the broader US hypoparathyroidism patient population without being able to ensure reliable and consistent supply. Takeda continues to work with urgency to test and evaluate approaches to best address these complex manufacturing and supply issues. Patients who are enrolled in the Special Use Program (SUP) continue to have access to NATPARA through that program.

We understand how difficult the past two years have been for the community, and all of us at Takeda remain committed to keeping the hypoparathyroidism community informed in the coming months and will provide another regulatory status update in March or April of 2022, after we hear back from the FDA.

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

Richard C. Ascroft, RPh, JD
Senior Vice President
Patient and Market Access
US Business Unit
**What is NATPARA® (parathyroid hormone) for Injection?**

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- 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 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

- **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

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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                                               Rick Ascroft
Head of U.S. Rare Disease Business Unit        Senior Vice President, Patient Services & Managed Markets
What is NATPARA® (parathyroid hormone) for Injection?

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- 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:
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  - fainting, dizziness, feeling lightheaded (low blood pressure)
  - fast heartbeat

• **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
March 31, 2021

Dear Valued Patient,

On behalf of Takeda, we are sharing the following NATPARA® (parathyroid hormone) for Injection information regarding the status of the NATPARA recall in the U.S.

As a patient previously prescribed NATPARA, we know that you are eager for an update about our plans to make NATPARA available again for appropriate patients with chronic hypoparathyroidism in the U.S. 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.

We are currently experiencing a manufacturing delay that 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. This manufacturing delay has further impacted our timelines, and at this time we do not expect a return to the U.S. market before March 31, 2022.

We recognize that this update may be difficult for those who have been eagerly awaiting information about our anticipated timelines for bringing NATPARA back. We are also disappointed that there is not better news to share with you. We encourage you to continue working with your health care team to determine how to best manage your condition during this extended period without NATPARA.

We plan to schedule a teleconference with the U.S. chronic hypoparathyroidism patient community in the coming weeks. Please watch for more information about that upcoming event in the NATPARA Updates section of our Takeda U.S. Newsroom at https://www.takeda.com/en-us/newsroom/natpara-updates/. Information should be posted during the week of April 5, 2021. We will also share the information with the Hypoparathyroidism Association.

Sincerely,

Cheryl Schwartz  Rick Ascroft
Head of U.S. Rare Disease Business Unit  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).
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- 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).

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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

**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
muscle weakness. These may be signs of too much calcium in your blood.

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?

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  – itching
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• 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.
February 5, 2021

Dear Valued Patient,

We’re sending you this letter because you are prescribed NATPARA (parathyroid hormone) 75-mcg or NATPARA 100-mcg through the Special Use Program and your OnePath® Patient Support Manager has been unable to reach you by phone.

We are providing you with this letter to inform you of a potential shipping delay. An inventory processing delay, compounded by a severe winter storm during the week of February 1, 2021, has impacted the NATPARA® 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, 2021.

**ACTION NEEDED:** Please contact your OnePath Patient Support Manager at 866-888-0660 at your earliest convenience so we can provide you with urgent information related to your NATPARA shipments and your prescribing physician.

We are in the process of communicating with all prescribing physicians to notify them about this inventory issue and shipping delay. If a new prescription is needed, based on your physician’s medical judgement, please make sure your prescribing physician contacts Takeda OnePath at 866-888-0660 as soon as possible. If your Physician has previously submitted an alternative back-up prescription form, that alternative prescription will be filled to avoid an interruption. Our goal is to supply you with the backup prescription that is on file, if needed. Your regular prescription will resume once that dose is again available. A Takeda OnePath® Patient Support Manager will follow up with you and answer questions related to the processing of this prescription or your scheduled shipments.

This shipping delay 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.

As a patient who is receiving NATPARA through the Special Use Program, we want to remind you 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 your ability to receive NATPARA product through the program.

It is important to remember that any potential interruption or reduction in the daily dose of NATPARA can cause a decrease in blood calcium levels (severe hypocalcemia) which can be dangerous. We appreciate your patience.
We recognize the important medical need that NATPARA fills for patients like you who are living with chronic hypoparathyroidism. We appreciate your patience.

Cynthia Schwartz                                         Rick Ascroft
Head of U.S. Rare Disease Business Unit      Senior Vice President, Patient Services & Managed Markets

What is NATPARA® (parathyroid hormone) for Injection?
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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

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December 22, 2020

Dear Valued Patient,

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. You will continue to receive NATPARA through the Special Use Program according to your current shipping schedule.

Your Takeda OnePath® Patient Support Manager will contact you 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 your next NATPARA shipment or the Special Use Program. If you have any immediate questions or concerns, please contact your Takeda OnePath® Patient Support Manager at 866-888-0660. Patient Support Managers are available Monday through Friday 8:30 AM – 8:00 PM ET.

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.

As a patient who is receiving NATPARA through the Special Use Program, we want to remind you 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 your ability to receive NATPARA product through the program.

Enclosed for your reference is the full NATPARA Prescribing Information and Medication Guide. For additional medical information, please contact your healthcare provider.

We recognize that we have been communicating about supply frequently since October 2020, and we are doing that to ensure that you and your prescriber 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

US-NAT-0356v1.0 12/20
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.

Wishing you and your family a happy and healthy holiday season,

Cheryl Schwartz                                                Daniel McNamara
Head of U.S. Rare Disease Business Unit      Head of U.S. Patient Services

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.

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
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.

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

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OnePath® is a registered trademark of Shire Human Genetic Therapies, Inc., a Takeda company.
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December 16th, 2020

Dear Valued Patient,

We are writing to provide the latest update regarding the potential for near-term supply interruptions of multiple doses of NATPARA® (parathyroid hormone) for Injection that may impact U.S. patients receiving NATPARA through the Special Use Program (SUP). While we work with urgency to avoid any supply interruptions for patients receiving NATPARA through the SUP, our priority is to ensure that you and your prescriber are prepared in the event of an actual supply interruption. Given the fluid nature of the situation, we could have additional information available as soon as the week of December 21, 2020.

If you are receiving NATPARA 100-mcg or NATPARA 75-mcg, please see the following time-sensitive information regarding the immediate actions you must take. If you are receiving other doses of NATPARA, there’s nothing you need to do at this time. However, supply status updates for all other NATPARA doses are also included in this letter.

*IMMEDIATE ACTION REQUIRED FOR PATIENTS RECEIVING NATPARA 75-MCG OR NATPARA 100-MCG*

If you have not yet contacted your prescribing physician to determine the best treatment plan for you, please contact him/her as soon as possible. Since our update during the week of November 16, 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. 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.

Based on your prescriber’s independent medical judgement, your revised treatment plan may require a new prescription. Please ensure you work closely with your prescribing physician on any changes to your treatment plan, including the potential for a new prescription.

**Please note that if you are currently receiving NATPARA 100-mcg or NATPARA 75-mcg and you have not received an updated prescription, or if your prescriber has provided a modified dose for NATPARA 100-mcg that includes the 75-mcg dose of NATPARA, please contact your physician as soon as possible. For patients receiving NATPARA 100-mcg, we would need to receive an updated prescription form from your physician by December 22, 2020 and if you are a patient receiving NATPARA 75-mcg, we would need to receive an updated prescription form by January 8, 2021 in order to continue to ship medication to you. Updated prescription forms not received by these dates will result in disruption in shipments to you.

However, if your physician has already submitted an updated prescription form in anticipation of a potential supply interruption, and that updated prescription does not include the 75-mcg dose of NATPARA, there’s nothing more you need to do. Your Takeda OnePath® Patient Support Manager will provide you with the shipment timing information for your updated prescription.

Patient safety is Takeda’s main priority and, as a patient enrolled in the Special Use Program who is receiving NATPARA 75-mcg or NATPARA 100-mcg, we are alerting you and your prescribing physician
that 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. It is important for you to work closely with your healthcare provider for important medical recommendations, including frequent monitoring of your blood calcium levels and close titration of active vitamin D and calcium supplements if you stop or alter your dose as a result of this supply interruption to avoid hypocalcemia.

**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 also communicated to physicians who have prescribed NATPARA 25-mcg or NATPARA 50-mcg that there is nothing they need to do at this time.

As a patient who is receiving NATPARA through the Special Use Program, we want to remind you 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 your ability to receive NATPARA product through the program.

OnePath will continue to work closely with your prescribing physician to support your treatment plan. If you have any immediate questions or concerns, please contact your Takeda OnePath® Patient Support Manager at 866-888-0660. Patient Support Managers are available Monday through Friday 8:30 AM – 8:00 PM ET.

Enclosed for your reference is the full NATPARA Prescribing Information and Medication Guide. For additional medical information, please contact your healthcare provider.

We recognize the important medical need that NATPARA fills for patients like you who are living with chronic hypoparathyroidism. As we have communicated previously, this is a fluid situation and we continue to work with urgency, and with US regulatory authority oversight, to avoid supply disruptions for patients receiving NATPARA through the SUP. We could have updated information regarding NATPARA 100-mcg and NATPARA 75-mcg as soon as the week of December 21, 2020 and will keep you updated as soon as new information is available. We appreciate your patience as we work to address these issues.

Sincerely,

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

Daniel McNamara  
Head of U.S. Patient Services
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

- 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

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Dear Valued Patient,

We are writing 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. We are also notifying you that we are now anticipating a near-term supply interruption of NATPARA 25-mcg, as well.

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.

If you are receiving NATPARA 25-mcg or NATPARA 100-mcg, please see the following time-sensitive information regarding the immediate actions you must take. If you are receiving other doses of NATPARA, there’s nothing you need to do at this time. However, supply status updates for all other NATPARA doses are also included in this letter.

*IMMEDIATE ACTION REQUIRED FOR PATIENTS RECEIVING NATPARA 25-MCG OR NATPARA 100-MCG*

If you have not yet contacted your prescribing physician to determine the best treatment plan for you, please contact him/her as soon as possible. NATPARA 25-mcg is expected to be unavailable due to a supply interruption as soon as December 8, 2020, and NATPARA 100-mcg is expected to be unavailable due to a supply interruption as soon as January 2, 2021. Based on your prescriber’s independent medical judgement, your revised treatment plan may require a new prescription. Please ensure you work closely with your prescribing physician on any changes to your treatment plan, including the potential for a new prescription.

Patient safety is Takeda’s main priority and, as a patient enrolled in the Single Use Program who is receiving NATPARA 25-mcg or NATPARA 100-mcg, we are alerting you and your prescribing physician that 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. It is important for you to work closely with your healthcare provider for important medical recommendations, including frequent monitoring of your blood calcium levels and close titration of active vitamin D and calcium supplements if you stop or alter your dose as a result of this supply interruption to avoid hypocalcemia.

NO IMMEDIATE ACTION REQUIRED FOR PATIENTS RECEIVING NATPARA 50-mcg or NATPARA 75-mcg:

At this time, we do not anticipate near-term supply interruptions for NATPARA 50-mcg or NATPARA 75-mcg doses before the end of 2020. However, we are closely monitoring these NATPARA doses and could experience supply interruptions in the event that manufacturing disruptions persist. We are committed to supply continuity and will provide you and your prescribing physician with an update on all NATPARA doses by mid-December.

Compliance with Special Use Program Terms & Conditions

As a patient who is receiving NATPARA through the Special Use Program, we want to remind you 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 your ability to receive NATPARA product through the program.

OnePath will continue to work closely with your prescribing physician to support your treatment plan. If you have any immediate questions or concerns, please contact your Takeda OnePath® Patient Support Manager at 866-888-0660. Patient Support Managers are available Monday through Friday 8:30 AM – 8:00 PM ET.

Enclosed for your reference is the full NATPARA Prescribing Information and Medication Guide. For additional medical information, please contact your healthcare provider.

We recognize the important medical need that NATPARA fills for patients like you who are living with chronic hypoparathyroidism. While we focus on limiting these supply interruptions for patients who are receiving NATPARA through the Special Use Program, we continue to prioritize the goal of safely bringing NATPARA back to the broader patient community with U.S. Regulatory Authority oversight.

Sincerely,

Cheryl Schwartz          Daniel McNamara
Head of U.S. Rare Disease Business Unit   Head of U.S. Patient Services

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.

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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

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Dear Valued Patient,

As a patient who is receiving NATPARA® (parathyroid hormone) for Injection through the Special Use Program (SUP), we are writing to inform you of an anticipated near-term supply interruption of NATPARA 100-mcg as early as November 21st, 2020.

If you are receiving NATPARA 100-mcg, please see the following time-sensitive information regarding the immediate actions you must take. If you are receiving other doses of NATPARA, there’s nothing you need to do at this time. However, supply status updates for all other NATPARA doses are also included in this letter.

**IMMEDIATE ACTION REQUIRED FOR PATIENTS RECEIVING NATPARA 100-mcg:**
Please contact your prescribing physician as soon as possible to determine the best treatment plan for you. Based on your prescriber’s independent medical judgement, your revised treatment plan may require a new prescription. Please ensure you work closely with your prescribing physician on any changes to your treatment plan, including the potential for a new prescription.

These supply interruptions were caused by unexpected manufacturing disruptions and are separate from the issue of rubber particulates originating from the rubber septum of the NATPARA cartridge. We deeply regret the interruption in supply and are making it a priority to bring product back quickly. At the same time, we are working on possible options for alternate treatment approaches with U.S. Regulatory Authority (U.S. Food & Drug Administration or “FDA”) oversight and will keep you and your prescribing physician informed.

Patient safety is Takeda’s main priority and, as a patient enrolled in the Single Use Program who is receiving NATPARA 100-mcg, we are alerting you and your prescribing physician that 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. It is important for you to work closely with your healthcare provider for important medical recommendations, including frequent monitoring of your blood calcium levels and close titration of active vitamin D and calcium supplements if you stop or alter your dose as a result of this supply interruption to avoid hypocalcemia.

**NO IMMEDIATE ACTION REQUIRED FOR PATIENTS RECEIVING NATPARA 25-mcg, NATPARA 50-mcg or NATPARA 75-mcg:**
At this time, we do not anticipate near-term supply interruptions for NATPARA 25-mcg, NATPARA 50-mcg or NATPARA 75-mcg doses. However, we are closely monitoring these NATPARA doses and could experience supply interruptions in the event that manufacturing disruptions persist. We are committed to supply continuity and will provide you and your prescribing physician with an update on the NATPARA 25-mcg, NATPARA 50-mcg and NATPARA 75-mcg doses by November 16, 2020.

**Compliance with Special Use Program Terms & Conditions**
As a patient who is receiving NATPARA through the Special Use Program, we want to remind you 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 could lead to loss of eligibility for the Special Use Program.

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Program (single dose use) could result in termination of your ability to receive NATPARA product through the program.

OnePath will be working closely with your prescribing physician to support your treatment plan. For patients receiving NATPARA 100-mcg, a Takeda OnePath representative will also be reaching out to you in the coming days to walk you through this update and align on next steps. If you have any immediate questions or concerns, please call OnePath at 866-888-0660 Monday through Friday 8:30 AM – 8:00 PM ET.

Enclosed for your reference is the full NATPARA Prescribing Information and Medication Guide. For additional medical information, please contact your healthcare provider.

We recognize the important medical need that NATPARA fills for patients like you who are living with chronic hypoparathyroidism. While we focus on limiting these supply interruptions for patients who are receiving NATPARA through the Special Use Program, we continue to prioritize the goal of safely bringing NATPARA back to the broader patient community with U.S. Regulatory Authority oversight.

Sincerely,

Cheryl Schwartz  
Daniel McNamara  
Head of U.S. Rare Disease Business Unit  
Head of U.S. Patient Services

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

NATPARA® is a registered trademark of Shire-NPS Pharmaceuticals, Inc., a Takeda company.
OnePath® is a registered trademark of Shire Human Genetic Therapies, Inc., a Takeda company.
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January 21, 2020

Dear Valued Patient,

On behalf of Takeda, I am writing to update you about the status of NATPARA in the US. We have worked closely with the Food and Drug Administration (FDA) over the last several months on our proposed plan to bring NATPARA back to patients. Based on data generated from additional testing and feedback from the FDA, it is now clear that additional product modifications and testing will be required that will significantly impact our timelines. While we are continuing to work toward resupply as quickly as possible, I am disappointed to share that the additional testing and potential device modifications will likely cause more than a year’s delay in bringing NATPARA back to US patients. We deeply regret this difficult news. Additional work is ongoing with the FDA, and we will continue to keep you informed as new information becomes available.

While we continue this critically important work, we are also committed to ensuring supply, through the Special Use Program, to patients previously prescribed NATPARA who are at extreme risk of life-threatening complications as a result of discontinuation of treatment. To date, 358 patients are receiving NATPARA at no cost as part of the Program, which was developed in collaboration with the FDA.

We understand that the Special Use Program is extremely limited and will not address the broader needs of patients who were previously prescribed NATPARA. As we have communicated previously, the Special Use Program requires that product usage be limited to a single dose per cartridge, instead of 14 doses per cartridge, to minimize the potential of particle formation caused by repeat punctures. This means that patients enrolled in the Special Use Program use one year’s worth of cartridges each month. Because of this, we must limit the Program to patients who are at significant risk of life-threatening complications to ensure supply for the most high-risk patients.

We know that this is not the news you were hoping to hear, and we recognize how difficult this interruption in therapy has been for you and your families. Our top priority, and our commitment to you all, is to continue to work with the FDA to identify all potential options for getting this critical medication back to you as quickly and as safely as we can.

Sincerely,

Cheryl Schwartz
Head of US Hematology & Rare Disease Business Unit
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).
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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.
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- 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.

SS3483 01/20
US Recall of NATPARA® (parathyroid hormone) for Injection

IMPORTANT INFORMATION FOR NATPARA PATIENTS

Dear Valued Patient,

The purpose of this letter is to share some new and important information regarding Takeda’s September 5, 2019 US recall for all doses of NATPARA® (parathyroid hormone) for Injection (25 mcg, 50 mcg, 75 mcg, and 100 mcg).

NATPARA is a parathyroid hormone currently approved in the US as the only adjunctive treatment for adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone (calcium and vitamin D).

On October 2nd, the US Food & Drug Administration (“US FDA”) informed Takeda that, following further review of the NATPARA recall, they are classifying NATPARA recall as Class I due to the potential risk of rubber stopper particles clogging the needle and leading to under-dosing. The Class I recall requires that all patients with product received prior to the recall of September 5, 2019 (“Recalled Product”) return their unused NATPARA to Takeda to prevent the use of Recalled Product. The safety profile of NATPARA remains consistent with the product label.

In parallel, Takeda continues to work closely with the US FDA regarding NATPARA, and values the US FDA’s collaboration and feedback as we work together to resupply NATPARA to patients who need it.

Based on the FDA’s classification, enclosed in this envelope you will find information from Stericycle, a third-party vendor that works with companies such as Takeda to coordinate product recalls. This includes instructions on how to return your unused NATPARA product using the Patient Return Kit.

With patient safety as the company’s main priority, Takeda is communicating directly with healthcare professionals, patients, and specialty pharmacies in the US regarding the actions required as a result of the Class I recall. Consistent with the product labelling, Takeda is alerting NATPARA patients and prescribers that discontinuing NATPARA abruptly can cause a sharp decrease in blood calcium levels (severe hypocalcemia) which can result in serious health consequences. It is critically important that patients contact their prescribing healthcare provider to discuss their individual treatment plan and ensure close supervision, including frequent monitoring of blood calcium levels and close titration of active vitamin D and calcium supplements upon stopping NATPARA to avoid low blood calcium (hypocalcemia).

It is critical to note that the Special Use Program is unaffected by the Class I recall and continues to support patients previously prescribed NATPARA who are at extreme risk of life-threatening complications as a result of discontinuation of NATPARA. This means that the
single-use NATPARA cartridges that you have received, or are expected to receive under the Special Use Program, are excluded from the Class I recall and you should continue to use them as prescribed by your physician.

Any patient who believes that they may qualify for the Special Use Program should contact their prescribing healthcare provider. Through this program, healthcare providers will be able to request NATPARA for extraordinary, life-threatening cases. This program requires a signed physician case report confirming the physician’s decision to prescribe NATPARA and their determination that without continued access to NATPARA the patient faces life-threatening health consequences. The prescribing physician and the Medical Review committee will then determine if a patient is at extreme medical risk and should have access to NATPARA. The Medical Review committee is evaluating eligibility on a case-by-case basis for patients who are at most risk for life-threatening complications.

All of us at Takeda understand the impact that this recall has on patients like you, and we will continue to work closely with the FDA until we are able to resolve the issue and resume supply.

To contact a OnePath Patient Support Manager, please call 1-866-888-0660. OnePath is available Monday through Friday, 8:30am to 8:00pm, Eastern Time.

Sincerely,

Daniel McNamara
Head of US Patient Services
Takeda Pharmaceutical Company Limited
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
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  – fainting, dizziness, feeling lightheaded (low blood pressure)

  – 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.
September 25, 2019

Dear Valued Patient,

We recognize that the NATPARA® recall in the US has been extremely difficult for patients, their families and caregivers. Since this began on September 5, 2019, our team has been working diligently with the FDA on a number of potential solutions to bring this critical medicine back to patients.

While we are in discussions with the FDA to reintroduce NATPARA to the broader patient community, Takeda and the FDA have developed 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, despite efforts to actively manage their condition. Through this program, healthcare providers will be able to request NATPARA for patients facing life-threatening complications.

It is anticipated that an extremely small number of patients prescribed NATPARA may be eligible for this limited program. Additional information about the Special Use Program for healthcare providers can be found here: https://www.takeda.com/en-us/newsroom/news-releases/2019/takeda-announces-natpara-special-use-program-in-the-us/. Physicians are also receiving detailed information about this new program.

Patients who have questions about their eligibility under the Special Use Program or about their individual treatment plans should consult with their NATPARA prescribing physician.

While this is an important first step, we realize this short-term and extremely limited program will not address the needs of the vast majority of patients. We have heard your frustration and want to assure you that we are working diligently with the FDA on both short-term and long-term solutions to bring NATPARA back to the broader patient community, which remains our highest priority.

We are dedicated to the hypoparathyroidism community and the resupply of NATPARA for patients. We will continue to work with the FDA on this issue and keep patients and healthcare providers informed as more information becomes available.

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.

Sincerely,

Dan McNamara
Head of US Patient Services
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)  Low blood calcium (hypocalcemia)

- 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.
- 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.

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

NATPARA® is a registered trademark of Shire-NPS Pharmaceuticals, Inc., a Takeda company.

OnePath® is a registered trademark of Shire Human Genetic Therapies, Inc., a Takeda company.

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S52117 09/19
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.

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?

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

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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 see Full Prescribing Information, Medication Guide, and Instructions for Use for NATPARA.
Message About the US NATPARA Recall

Cambridge, MA, September 13, 2019 --- On September 5, 2019, Takeda 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 being conducted after discussions with the FDA, which has classified it as a Pharmacy Level recall due to the potential for rubber particulate from the rubber septum component part of the NATPARA cartridge to enter into the drug solution. Patients do not need to return or discard the NATPARA they have on-hand. But, it is imperative that patients immediately see their healthcare provider before stopping NATPARA. Doing so will help patients discontinue the medicine as safely as possible, in a supervised setting, including frequent monitoring of blood calcium levels and close titration of active vitamin D and calcium supplements upon stopping NATPARA to avoid low blood calcium. You can read more information about the NATPARA recall here.

We recognize that the recall has been extremely difficult for our NATPARA patients and their families. Since the recall began on September 5, 2019, our dedicated OnePath team has reached out to the more than 2,000 NATPARA patients in the US with information and support. Our commitment to patients remains our highest priority. We are working urgently with the FDA on a number of potential solutions to bring this critical medicine back to patients as quickly as possible and will continue to keep patients and healthcare providers informed.

If you are a patient with questions, please reach out to our OnePath patient services team at 866-888-0660. Healthcare providers with questions should call 800-828-2088.

We are committed to resolving this critical issue quickly and sincerely regret the impact this recall is having on patients and their families, as well as the broader hypoparathyroidism community.

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).
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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 http://www.fda.gov/medwatch or call 1-800-FDA-1088.

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

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Important Notice

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About Takeda Pharmaceutical Company Limited

Takeda Pharmaceutical Company Limited (TSE:4502/NYSE:TAK) is a global, values-based, R&D-driven biopharmaceutical leader headquartered in Japan, committed to bringing Better Health and a Brighter Future to patients by translating science into highly-innovative medicines. Takeda focuses its R&D efforts on four therapeutic areas: Oncology, Gastroenterology (GI), Rare Diseases and Neuroscience. We also make targeted R&D investments in Plasma-Derived Therapies and Vaccines. We are focusing on developing highly innovative medicines that contribute to making a difference in people's lives by advancing the frontier of new treatment options and leveraging our enhanced collaborative R&D engine and capabilities to create a robust, modality-diverse pipeline. Our employees are committed to improving quality of life for patients and to working with our partners in health care in approximately 80 countries and regions.

For more information, visit https://www.takeda.com.
September 6, 2019

US Recall of NATPARA® (parathyroid hormone) for Injection

IMPORTANT INFORMATION REQUIRING ACTION

Dear Valued Patient,

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. The safety profile of NATPARA remains consistent with the product label. As of the date of this recall, Takeda is not aware of any adverse events directly related to this matter. After discussions with the US FDA, the company is issuing this recall as a precaution.

NATPARA is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.

This recall 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.

It is critically important that you contact your prescribing healthcare provider, who has also received this important information. As part of this communication, and consistent with the product label, we are alerting NATPARA patients and prescribers that stopping NATPARA abruptly can cause a sharp decrease in blood calcium levels (severe hypocalcemia) which can have serious health consequences. You need to be under close supervision by your healthcare provider to discuss your individual treatment plan, including frequent monitoring of your blood calcium levels and close titration of active vitamin D and calcium supplements upon stopping NATPARA to avoid low blood calcium (hypocalcemia).
In addition, a OnePath® Patient Support Manager will be contacting you to answer any questions you may have about the content of this letter.

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.

We sincerely regret the impact this interruption has on you.

To contact a OnePath Patient Support Manager, please call 1-866-888-0660. OnePath is available Monday through Friday, 8:30am to 8:00pm, Eastern Time.

Sincerely,

Daniel McNamara
Head of US Patient Services
Takeda Pharmaceutical Company Limited

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.

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

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