<LOC Address>

<Date [DD/MM/YYYY]>

Natpar (parathyroid hormone): Discontinuation of manufacturing at the end of 2024 and update on 100mcg shortage

Marketing Authorisation Number: EU/1/15/1078/001, EU/1/15/1078/002, EU/1/15/1078/003, EU/1/15/1078/004

Dear Healthcare Professional,

Takeda, in agreement with the European Medicines Agency and the <National Competent Authority> would like to inform you of the following:

Summary

- **Manufacturing of all strengths of Natpar will be discontinued globally at the end of 2024, due to unresolved manufacturing challenges. This means that Natpar will be withdrawn from the global market.**
- **Beyond 2024, Takeda intends to supply available doses until inventory is depleted or expired. Takeda will provide updates before the manufacturing end date and ahead of any further potential supply interruptions.**
- **A shortage of the 100 mcg/dose strength will continue until the discontinuation of manufacturing. Healthcare professionals can prescribe an alternative dosing regimen of Natpar, as per their clinical judgment (see details below).**
- **When changing the dosing or discontinuing Natpar, it is essential to closely monitor serum calcium levels and to monitor patients for signs and symptoms of hypocalcemia, while carefully adjusting active vitamin D and supplemental calcium doses in all patients.**
- **Healthcare professionals are advised <u>not to initiate any new patients on any strength of Natpar.</u>**

Background

- Natpar is indicated as adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone.
- Takeda has decided to discontinue manufacturing of all strengths of Natpar from end of 2024 due to unresolved manufacturing issues.

- The 100 mcg/dose strength shortage will continue until the discontinuation of manufacturing.
- Takeda will provide updates before the manufacturing end date in late 2024 and ahead of any potential supply interruptions.

Alternative dosing options for patients currently on Natpar 100 mcg/dose remain unchanged since our communication dated <insert locally>.

Alternative dosing options

For patients already on Natpar 100 micrograms/dose, Takeda would like to make you aware of the following alternative dosing options:

- Multiple dosing: If HCPs believe, in their clinical judgement, a 100 micrograms dose is necessary for their patients, they can prescribe two separate injections of Natpar 50 micrograms/dose. If the HCP decides to prescribe 2 consecutive doses of Natpar 50 micrograms/dose, the second dose should be administered in the contralateral thigh using a new needle within 15 minutes of the first dose. HCPs must monitor serum calcium levels and adjust, if necessary, exogenous calcium and/or active vitamin D dosing.

  Or

- Reduced dosing: Natpar 75 micrograms/dose remains available for whom, in the HCP's clinical judgement, a reduced dose of Natpar 75 micrograms is appropriate. HCPs must monitor serum calcium levels and adjust, if necessary, exogenous calcium and/or active vitamin D dosing.

It is imperative that the attached updated patient information, *'Patient/Caregiver Injection Instructions for Natpar 100 micrograms/dose shortage'* is given to the patient and that the patient is sufficiently educated. HCPs should go through the patient education materials with the patient, to make sure they are understood.

For patients receiving 2 x Natpar 50 micrograms/dose, make sure to communicate the following:

One dose of Natpar 50 micrograms/dose should be injected in each thigh. A new needle should be used for each injection and the dose indicator checked to confirm two doses of 50mcg have been administered. To reduce the chance of local reactions, the injections should alternate between upper and lower parts of the thighs each day. The two doses should be taken less than 15 minutes apart; however, if the patient by error takes only one dose, they should take the second dose as soon as possible and contact their doctor. The patient must be educated on the importance of correct dosing, and to contact the HCP in case of any error in dosing.

For patients where the dose is reduced from Natpar 100 micrograms/day to Natpar 75 micrograms/day, make sure to communicate the following:

The reduction in dose places the patient at increased risk of hypocalcaemia. This must be communicated to the patient, informing them of the signs of hypocalcaemia and on when they should inform their doctor.

For all patients affected by the 100micrograms/day drug shortage:

It is essential to closely monitor serum calcium levels and observe for signs and symptoms of hypocalcemia while carefully adjusting active vitamin D and supplemental calcium doses in any patient if Natpar dosing is changed. Please review the SmPC Section 4.2 (Interruption or discontinuation of treatment) and Section 4.4 (Warnings and Precautions: Hypocalcaemia).

No new patients on Natpar:

The manufacturing of all strengths of Natpar will be discontinued at the end of 2024. In order to ensure that existing patients can continue to receive treatment, HCPs are asked not to initiate any new patients **on any strength of Natpar**.

Call for reporting

Please report any adverse events experienced by your patients taking Natpar. When reporting, please provide as much information as possible including information about batch details, medical history, any concomitant medication, onset, and treatment dates.

Please report suspected adverse reactions with any medicine or vaccine to the <Competent Health Authority (e.g. Website, email, Address, Contact no.)>

Adverse events should also be reported to Takeda: <insert local contact details>

Company Contact Point

For questions relating to the content of this communication please contact the Takeda Medical Information Department:

medinfoEMEA@takeda.com

<Insert LOC contact phone and email>

Marketing Authorization Holder
Takeda Pharmaceuticals International AG Ireland Branch
Block 3, Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
D02 Y754
Ireland

Yours faithfully,
<Local Takeda affiliate representative>

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Natpar (parathyroid hormone)
Marketing authorisation holder(s)	Takeda Pharmaceuticals International AG Ireland Branch
Safety concern and purpose of the communication	To inform prescribing physicians of manufacturing production end date at end of 2024, the 100mcg strength not being reintroduced and the current status of continuing supply of 75, 50 and 25mcg until further notice of stock availability
DHPC recipients	Prescribing physicians, endocrinologists to be confirmed by local commercial teams. Patient Advocacy Groups to be identified and included. Pharmacy chains where applicable.
Member States where the DHPC will be distributed	In all EEA member states where Natpar is distributed, whether commercially or via clinical trials or named patient programs

Timetable	Date
DHPC and communication plan (in English) agreed by CHMP/CMDh	26 September 2022
Submission of translated DHPCs to the national competent authorities for review	26 September 2022
Agreement of translations by national competent authorities	29 September 2022
Dissemination of DHPC	04 October 2022

Appendix to DHPC: Patient/Caregiver Injection Instructions
for Natpar 100 micrograms/dose shortage

Background

We previously advised of a shortage of Natpar 100micrograms/dose, from June 2022 for a period of at least six months. Due to unresolvable manufacturing challenges, Takeda will no longer be able to supply the Natpar 100 micrograms/dose strength and the dose strength will be unavailable on a permanent basis. This letter contains important information regarding how to handle the changes in the administration of Natpar due to the drug shortage of Natpar 100 micrograms/dose.

Your doctor will adjust your treatment in agreement with you. There are two alternative dosing options for substituting the Natpar 100 micrograms/dose injection:

1. If your doctor recommends <u>two (2) consecutive Natpar 50 micrograms/dose injections</u>:

This information applies if you previously were prescribed Natpar 100 micrograms/day and your doctor has decided that you should receive two (2) consecutive injections of Natpar 50 micrograms/day from the same cartridge as a result of the drug shortage.

If you are prescribed two injections of Natpar 50 micrograms/dose per day by your doctor, a new cartridge will need to be prepared every 7 days.

The two (2) doses should be given from one cartridge within 15 minutes as follows:

1. Gather two disposable pen needles.
2. Ensure you have properly cleaned the surface with disinfectant/alcohol pads before you begin.
3. Follow the steps in the package leaflet to administer the first injection of Natpar 50 micrograms/dose in the left thigh. To minimize the risk of reactions at the site of injections, you should alternate between upper and lower parts of the thighs each day.
4. Remove the needle from the device, and discard in accordance with the instructions in the package leaflet.
5. Choose a second injection site on the right thigh, clean the site with an alcohol pad and let it dry. To minimize the risk of reactions at the site of injections, you should alternate between upper and lower parts of the thighs each day.
6. Follow the steps in the package leaflet again to perform another injection of Natpar 50 micrograms/dose, now in the right thigh, within 15 minutes of the first injection.
7. Remove the needle from the device, and discard in accordance with the instructions in the package leaflet
8. Check the cartridge dose indicator to confirm 2 doses of 50 micrograms/dose have been delivered from the cartridge

<u>Note</u>: To avoid the risk of infection, it is very important to clean the injection sites with alcohol pads and ensure the surface where the Natpar pen device is placed has been thoroughly cleaned. Remember to perform the second injection within 15 minutes at a new, cleaned injection site on the alternate thigh.

The package leaflet states that you should only take 1 dose of Natpar. However, since your doctor has prescribed two (2) injections of Natpar 50 micrograms/dose, you should take 2 doses. The second dose should be administered as soon as possible after the first, but no more than 15 minutes later.

You may have side effects related to low or high levels of calcium in your blood (see section on side effects). You may be given medicines to treat or help prevent these side effects, or you may be asked to stop some of the medicines you are taking. These medicines include calcium or vitamin D. If your symptoms are severe, your doctor may give you additional medical treatment. Your doctor may choose to monitor your calcium levels more closely.

If you are injecting two doses per day, you may experience more reactions in the injection site as each thigh is injected daily. You should decrease this risk by alternately injecting in the upper and lower part of the thighs. If you get any reactions at the injection site, please contact your doctor or pharmacist.

If you forget a dose of Natpar.
If you forget to use Natpar (or cannot inject it at your usual time), administer your injections as soon as you can but do not inject more than the prescribed number of doses in the same day.
Take your next dose of Natpar at the usual time the next day. You may need to take more calcium supplements if you have signs of low blood calcium; see section on side effects.

If you accidentally take only one dose of Natpar 50 micrograms/dose instead of 2 doses of Natpar 50 micrograms/dose, and more than 15 minutes has passed since the first dose, inject the second dose of Natpar 50 micrograms/dose in the other thigh as soon as possible. Contact your doctor or pharmacist and take two (2) doses of Natpar 50 micrograms/dose the next day as planned.

If you take more Natpar than you should
If you, by mistake, inject 3 or more doses of Natpar 50 micrograms/day in a day, contact your doctor or pharmacist immediately.

2. If your doctor recommends Natpar <u>75 micrograms/dose injection</u>:

This information applies if you were previously prescribed Natpar 100 micrograms/day and your doctor has decided that you should receive Natpar 75 micrograms/day as a result of the drug shortage. Since your dose of Natpar has been reduced, you are receiving less Natpar than you did before the drug shortage.

You may have side effects related to low or high levels of calcium in your blood (see section on side effects). You may be given medicines to treat or help prevent these side effects, or you may be asked to stop some of the medicines you are taking. These medicines include calcium or vitamin D. If your symptoms are severe, your doctor may give you additional medical treatment. Your doctor may choose to monitor your calcium levels more closely. Pay special attention to the symptoms associated with low levels of calcium since reduction in dose increases this risk.

If you are prescribed Natpar 75 micrograms/dose, follow the instructions for injection as described in the package leaflet.

This section applies to <u>all patients</u>:

Possible side effects
A change in your dosing can **increase the risk of high blood calcium and/or low blood calcium**. Symptoms related to high or low calcium levels are included in the list below. If you experience any of these side effects, **contact your doctor right away**.

The following potentially serious side effects can occur when using Natpar:

- Very common: **high** levels of calcium in your blood, which can occur more often when you start treatment with Natpar.
- Very common: **low** levels of calcium in your blood; this can occur more often if you suddenly stop taking Natpar or in case of dose reduction.

Other side effects include:
Very common (may affect more than 1 in 10 people):

- headaches*,†
- tingling and numbness of the skin†
- diarrhea*,†
- nausea and vomiting*
- joint pain*
- muscle spasms†

Common (may affect up to 1 in 10 people):

- feeling nervous or anxious†
- sleep problems (feeling sleepy during the day or having trouble sleeping at night)*
- fast or uneven heartbeat*†
- high blood pressure*
- cough†
- stomach pain*
- muscle twitching or cramping†
- pain in your muscles†
- neck pain†
- pain in your arms and legs
- increased level of calcium in your urine*
- need to pass urine often†
- fatigue and lack of energy*
- chest pain
- redness and pain at injection site
- thirst*
- antibodies (produced by your immune system) to Natpar
- in blood tests, your doctor may see decreased levels of vitamin D and magnesium†

Not known (frequency cannot be estimated from the available data):

- allergic reactions (hypersensitivity), such as: swelling of the face, lips, mouth, or tongue; shortness of breath; itching; rash; hives
- seizures (fits) due to low levels of calcium in your blood†

*These side effects may be related to **high** levels of calcium in your blood.
†These side effects may be related to **low** levels of calcium in your blood.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system at <insert local information>. By reporting side effects, you can help provide more information on the safety of this medicine.

Questions
If you have any questions regarding the use of Natpar, please contact the doctor who prescribed Natpar for you.