<LOC Address>

<Date [DD/MM/YYYY]>

Natpar (parathyroid hormone) 100 micrograms/dose powder and solvent for solution for injection: expected shortage from June 30th, 2022

Marketing Authorisation Number 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

- **Due to manufacturing challenges, Takeda will be unable to supply the 100 micrograms/dose strength from approximately end of June 2022. The duration is unknown but is expected to last at least 6 months.**
- **Healthcare professionals are advised not to initiate any new patients on any strength of Natpar until the supply issue is resolved.**
- **For existing patients on 100 mcg once a day, once the 100 micrograms / dose strength is unavailable, healthcare professionals can prescribe an alternative dosing regimen, as per their independent clinical judgment (see details below).**
- **It is very important to closely monitor serum calcium levels and observe patients for signs and symptoms of hypocalcemia while carefully adjusting active vitamin D and supplemental calcium doses in all patients affected by Natpar 100 micrograms/dose shortage.**

Background on the concern

Natpar is indicated as adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone. Due to manufacturing challenges, Takeda will be unable to supply the 100 micrograms/dose strength from approximately end of June 2022. The duration is unknown but is expected to last at least 6 months.

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 independent 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 should consider monitoring of serum calcium levels and adjustment, as necessary, of exogenous calcium and/or active vitamin D.

  Or

- Reduced dosing: Natpar 75 micrograms/dose remains available for whom, in the HCP's independent clinical judgement, a reduced dose of Natpar 75 micrograms is appropriate. HCPs should consider monitoring of serum calcium levels and adjustment, as necessary, of exogenous calcium and/or active vitamin D.

It is imperative that the attached 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 hypocalcemia. 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 drug shortage:

It is very important 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 affected by the Natpar 100 micrograms/dose shortage. Please review the SmPC Section 4.2 (Interruption or discontinuation of treatment) and Section 4.4 (Warnings and Precautions: Hypocalcemia).

No new patients on Natpar:

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**.

There is a possibility that the 75 micrograms / dose strength may be similarly affected by a shortage later in 2022, so this should also be considered as part of the decision to choose an alternate dosing option as detailed above. Should a shortage occur for the 75 micrograms / dose, further communications will be issued to HCPs, to allow them to manage patients appropriately.

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>

Communication Plan for Direct Healthcare Professional Communication

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 the upcoming shortage of Natpar 100mcg and potential options to remediate risk to patients
DHPC recipients	Prescribing physicians including 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	22 April 2022
Submission of translated DHPCs to the national competent authorities for review	25 April 2022
Agreement of translations by national competent authorities	27 April 2022
Dissemination of DHPC	29 April 2022

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

Background

Due to manufacturing challenges, Takeda will be unable to supply the Natpar 100 micrograms/dose strength from approximately end of June 2022. The duration of the shortage is not known but is expected to last for at least six (6) months. 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 listed in Appendix V. 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.