SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Natpar 75 micrograms/dose powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Natpar 75 micrograms

Each dose contains 75 micrograms parathyroid hormone (rDNA) in 71.4 microlitre solution following reconstitution.

Each cartridge contains 1050 micrograms parathyroid hormone (rDNA).

*Parathyroid hormone (rDNA), produced in *E. coli* using recombinant DNA technology, is identical to the 84 amino acid sequence of endogenous human parathyroid hormone.

Excipient(s) with known effect

Each dose contains 0.32 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white and the solvent is a clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Natpar is indicated as adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone.

4.2 Posology and method of administration

General

Treatment should be supervised by a physician or other qualified healthcare professional experienced in the management of patients with hypoparathyroidism.

The goal of treatment with Natpar is to achieve calcaemic control and to reduce symptoms (see also section 4.4). The optimisation of parameters of calcium-phosphate metabolism should be in line with current therapeutic guidelines for the treatment of hypoparathyroidism.

Prior to initiating and during treatment with Natpar:

- Confirm 25-OH vitamin D stores are sufficient.
- Confirm serum magnesium is within the reference range.

Posology

Initiating Natpar

1. Initiate treatment with 50 micrograms once daily as a subcutaneous injection in the thigh (alternate thigh every day). If pre-dose serum calcium is >2.25 mmol/L, a starting dose of 25 micrograms can be considered.
2. In patients using active vitamin D, decrease the dose of active vitamin D by 50%, if pre-dose serum calcium is above 1.87 mmol/L.
3. In patients using calcium supplements, maintain calcium supplement dose.
4. Measure pre-dose serum calcium concentration within 2 to 5 days. If pre-dose serum calcium is below 1.87 mmol/L or above 2.55 mmol/L, this measurement should be repeated the following day.
5. Adjust dose of active vitamin D or calcium supplement or both based on serum calcium value and clinical assessment (i.e., signs and symptoms of hypocalcaemia or hypercalcaemia). Suggested adjustments to Natpar, active vitamin D and calcium supplements based on serum calcium levels are provided below:

4.3 Contraindications

Natpar is contraindicated in patients:

- with hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- who are receiving or who have previously received radiation therapy to the skeleton
- with skeletal malignancies or bone metastases
- who are at increased baseline risk for osteosarcoma such as patients with Paget's disease of bone or hereditary disorders
- with unexplained elevations of bone-specific alkaline phosphatase
- with pseudohypoparathyroidism.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and batch number of the administered product should be clearly recorded.

The aim of treatment with Natpar is to achieve a pre-dose serum calcium concentration of 2.0-2.25 mmol/L and an 8-12 hour post-dose serum calcium concentration <2.55 mmol/L.

Monitoring of patients during treatment
Pre-dose and in some cases post-dose serum calcium levels must be monitored during treatment with Natpar (see section 4.2). In a multi-centre clinical trial, albumin-corrected serum calcium (ACSC) values 6-10 hours post-dose were on average 0.25 mmol/L higher than the pre-dose values, with a maximum increase observed of 0.7 mmol/L. Calcium, vitamin D, or Natpar doses may need to be reduced if post-dose hypercalcaemia is observed, even if pre-dose calcium concentrations are acceptable (see section 4.2).

Hypercalcaemia
Hypercalcaemia was reported in clinical trials with Natpar. Hypercalcaemia commonly occurred during the titration period, during which doses of oral calcium, active vitamin D, and Natpar were being adjusted. Hypercalcaemia may be minimised by following the recommended dosing, the monitoring information, and asking patients about any symptoms of hypercalcaemia. If severe hypercalcaemia (>3.0 mmol/L or above upper limit of normal with symptoms) develops, hydration and temporarily stopping Natpar, calcium and active vitamin D should be considered until serum calcium returns to the normal range. Then consider resuming Natpar, calcium and active vitamin D at lower doses (see sections 4.2 and 4.8).

Hypocalcaemia
Hypocalcaemia, a common clinical manifestation of hypoparathyroidism, was reported in clinical trials with Natpar. Most of the hypocalcaemic events occurring in the clinical trials were mild to moderate in severity. In the post-marketing setting, cases of symptomatic hypocalcaemia, including cases that resulted in seizures, have been reported in patients being treated with Natpar. The risk for serious hypocalcaemia is highest after Natpar is withheld, missed or abruptly discontinued, but can occur at any time. Temporary or permanent discontinuation of Natpar must be accompanied by monitoring of serum calcium levels and increase of exogenous calcium and/or active vitamin D sources as necessary. Hypocalcaemia may be minimised by following the recommended dosing, the monitoring information, and asking patients about any symptoms of hypocalcaemia (see sections 4.2 and 4.8).

Concomitant use with cardiac glycosides
Hypercalcaemia of any cause may predispose to digitalis toxicity. In patients using Natpar concomitantly with cardiac glycosides (such as digoxin or digitoxin), monitor serum calcium and cardiac glycoside levels and patients for signs and symptoms of digitalis toxicity (see section 4.5).

Severe renal or hepatic disease
Natpar should be used with caution in patients with severe renal or hepatic disease because they have not been evaluated in clinical trials.

Use in young adults
Natpar should be used with caution in young adult patients with open epiphyses as these patients may be at increased risk for osteosarcoma (see section 4.3).

Use in elderly patients
Clinical studies of Natpar did not include sufficient numbers of subjects aged 65 and over to determine whether response in these subjects is different from younger subjects.

Tachyphylaxis
The calcium-raising effect of Natpar may diminish over time in some patients. The response of serum calcium concentration to administration of Natpar should be monitored at intervals to detect this and the diagnosis of tachyphylaxis considered.

If serum concentration of 25-OH vitamin D is low then appropriate supplementation may restore serum calcium response to Natpar (see section 4.2).

Urolithiasis
Natpar has not been studied in patients with urolithiasis. Natpar should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

Hypersensitivity
There have been post-marketing reports of hypersensitivity reactions in patients taking Natpar. Hypersensitivity reactions can include anaphylaxis, dyspnoea, angioedema, urticaria, rash, etc. If signs or symptoms of a serious hypersensitivity reaction occur, treatment with Natpar should be discontinued and hypersensitivity

reaction should be treated according to the standard of care. Patients should be monitored until signs and symptoms resolve (see sections 4.3 and 4.8). If Natpar is to be discontinued, monitoring for hypocalcaemia is necessary (see section 4.2).

Sodium Content
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The inotropic effects of cardiac glycosides are affected by serum calcium levels. Combined use of Natpar and cardiac glycosides (e.g., digoxin or digitoxin) may predispose patients to digitalis toxicity if hypercalcaemia develops. No drug-drug interaction study has been conducted with cardiac glycosides and Natpar (see section 4.4).

For any drug that affects serum calcium levels (e.g., lithium, thiazides), patients' serum calcium levels should be monitored.

Co-administration of alendronic acid and Natpar may lead to a reduction in the calcium sparing effect, which can interfere with the normalisation of serum calcium. Concomitant use of Natpar with bisphosphonates is not recommended.

Natpar is a protein that is not metabolised by and does not inhibit hepatic microsomal drug-metabolising enzymes (e.g., cytochrome P450 isoenzymes). Natpar is not protein bound and has a low volume of distribution.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no data from the use of Natpar in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

A risk to the pregnant woman or developing foetus cannot be excluded. A decision must be made whether to initiate or discontinue treatment with Natpar during pregnancy taking into account the known risks of therapy versus the benefit for the woman.

Breast-feeding

It is unknown whether Natpar is excreted in human milk.

Available pharmacology data in animals have shown excretion of Natpar in milk (see section 5.3).

A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue therapy with Natpar, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of Natpar on human fertility. Animal data do not indicate any impairment of fertility.

4.7 Effects on ability to drive and use machines

Natpar has no or negligible influence on the ability to drive and use machines. Since neurologic symptoms may be a sign of uncontrolled hypoparathyroidism, patients with disturbances in cognition or attention should be advised to refrain from driving or using machines until symptoms have subsided.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions among patients treated with Natpar were hypercalcaemia, hypocalcaemia, and their associated clinical manifestations including headache, diarrhoea, vomiting, paraesthesia, hypoaesthesia and hypercalciuria. In the clinical studies, these reactions were generally mild to moderate in severity and transient, and were managed with adjustments of Natpar, calcium and/or active vitamin D doses (see sections 4.4 and 5.1).

Tabulated list of adverse reactions

Adverse reactions for Natpar-treated patients in the placebo-controlled study and in post-marketing experience are listed below by MedDRA system organ class and frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), and not known (cannot be estimated from the available data). All adverse reactions identified in post-marketing experience are *italicised*.

System organ class	**Very common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Not known** (cannot be estimated from the available data)
Immune system dysorders			*Hypersensitivity reactions, (dyspnoea,*

			angioedema, urticaria, rash)
Metabolism and nutrition disorders	hypercalcaemia, hypocalcaemia	hypomagnesaemia†, tetany†	
Psychiatric disorders		anxiety†, insomnia*	
Nervous system disorders	headache*,†, hypoaesthesia†, paraesthesia†	somnolence*	
Cardiac disorders		palpitations*,†	
Vascular disorders		hypertension*	
Respiratory, thoracic and mediastinal disorders		cough†	
Gastrointestinal disorders	diarrhoea*,†, nausea*, vomiting*	abdominal pain upper*	
Musculoskeletal and connective tissue disorders	arthralgia*, muscle spasms†	muscle twitching†, musculoskeletal pain†, myalgia†, neck pain†, pain in extremity	
Renal and urinary disorders		hypercalciuria*, pollakiuria†	
General disorders and administration site conditions		asthenia*, chest pain†, fatigue, injection site reactions, thirst*	
Investigations		anti-PTH antibody positive, blood 25-hydroxycholecalciferol decreased†, vitamin D decreased	

*Signs and symptoms potentially associated with hypercalcaemia that were observed in the clinical trials.
†Signs and symptoms potentially associated with hypocalcaemia that were observed in the clinical trials.

Description of selected adverse reactions
Hypercalcaemia and hypocalcaemia were commonly encountered during the dose titration period. The risk for serious hypocalcaemia was greatest after the withdrawal of Natpar. Cases of hypocalcaemia resulting in seizures have been reported post-marketing (see section 4.4).

Injection site reactions
In the placebo-controlled study, 9.5% (8/84) Natpar-treated patients and 15% (6/40) placebo-treated patients experienced an injection site reaction, all of which were mild or moderate in severity.

Immunogenicity
Consistent with the potentially immunogenic properties of medicinal products containing peptides, administration of Natpar may trigger the development of antibodies. In the placebo-controlled study in adults with hypoparathyroidism, the

incidence of anti-parathyroid hormone (PTH) antibodies was 8.8% (3/34) and 5.9% (1/17) in patients who received subcutaneous administration of 50 to 100 micrograms Natpar or placebo once daily for 24 weeks, respectively.

Across all clinical studies in patients with hypoparathyroidism following treatment with Natpar for up to 7.4 years, the immunogenicity incidence rate was 16/87 (18.4%) and did not appear to increase over time. These 16 patients had low titre anti-PTH antibodies and, of these, 12 subsequently became antibody negative. The apparent transient nature of antibodies to PTH is likely due to the low titre. Two of these patients had antibodies with neutralising activity; these patients maintained a clinical response with no evidence of immune-related adverse reactions.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdose can cause hypercalcaemia, the symptoms of which may include heart palpitations, ECG changes, hypotension, nausea, vomiting, dizziness and headache. Severe hypercalcaemia may be a life-threatening condition requiring urgent medical care and careful monitoring (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium homeostasis, parathyroid hormones and analogues, ATC code: H05AA03

Mechanism of action
Endogenous parathyroid hormone (PTH) is secreted by the parathyroid glands as a polypeptide of 84 amino acids. PTH exerts its action via cell-surface parathyroid hormone receptors, present in bone, kidney and nerve tissue. Parathyroid hormone receptors belong to the family of G-coupled protein receptors.

PTH has a variety of critical physiological functions that include its central role in modulating serum calcium and phosphate levels within tightly regulated levels, regulating renal calcium and phosphate excretion, activating vitamin D, and maintaining normal bone turnover.

Natpar is produced in *E. coli* using recombinant DNA technology, and is identical to the 84 amino acid sequence of endogenous human parathyroid hormone.

Pharmacodynamic effects

PTH (1-84) is the principal regulator of plasma calcium homeostasis. In the kidney, PTH (1-84) increases renal tubular reabsorption of calcium and promotes phosphate excretion.

The overall effect of PTH is to increase serum calcium concentration, to reduce urinary excretion of calcium and to lower serum phosphate concentration.

Natpar has the same primary amino acid sequence as endogenous parathyroid hormone and may be anticipated to have the same physiological actions.

Clinical efficacy and safety

The safety and clinical efficacy of Natpar in adults with hypoparathyroidism is derived from 1 randomised, placebo-controlled study and an open-label extension study. In these studies, Natpar was self-administered, with daily doses ranging from 25 to 100 micrograms per subcutaneous injection.

Study 1 – REPLACE

The objective of this trial was to maintain serum calcium with Natpar while reducing or replacing oral calcium and active vitamin D. The study was a 24-week, randomised, double-blind, placebo-controlled, multicentre trial. In this trial, patients with chronic hypoparathyroidism receiving calcium and active forms of vitamin D (vitamin D metabolite or analogues) were randomised to Natpar (n=84) or placebo (n=40). The mean age was 47.3 years (range 19 to 74 years); 79% were females. Patients had hypoparathyroidism for an average of 13.6 years.

At randomisation, active forms of vitamin D were reduced by 50% and patients were allocated to Natpar 50 micrograms daily or placebo. Randomisation was followed by a 12-week Natpar titration phase and a 12-week Natpar dose maintenance phase.

Ninety percent of patients who were randomised completed 24 weeks of treatment.

For the efficacy analysis, subjects that fulfilled three components of a three-part response criterion were considered responders. A responder was defined using a composite primary efficacy endpoint of at least a 50% reduction from the baseline active vitamin D dose AND at least a 50% reduction from the baseline oral calcium AND an albumin-corrected total serum calcium concentration maintained or normalised compared with the baseline value ($\geq$1.875 mmol/L) and did not exceed the upper limit of the laboratory normal range.

At the end of treatment, 46/84 (54.8%) patients treated with Natpar achieved the primary endpoint versus 1/40 (2.5%) with placebo ($p<0.001$).

At Week 24, for patients who completed the study, 34/79 (43%) Natpar patients were independent of active vitamin D treatment and were receiving no more than 500 mg of calcium citrate, compared with 2/33 (6.1%) placebo patients ($p<0.001$).

Sixty-nine percent (58/84) of subjects randomised to Natpar showed a reduction in oral calcium of ≥50% compared to 7.5% (3/40) of subjects randomised to placebo. The mean percent change from baseline in oral calcium was -51.8% (SD 44.6) in subjects receiving Natpar compared to 6.5% (SD 38.5) in the placebo group ($p<0.001$). In addition, 87% (73/84) of patients treated with Natpar showed a ≥50% reduction in oral active vitamin D versus 45% (18/40) in the placebo group.

Study 2 – RACE

Study 2 is a six year long-term, open-label extension study of daily subcutaneous dosing of Natpar in hypoparathyroidism subjects who completed prior studies with Natpar.

A total of 49 subjects were enrolled in the study. Subjects received doses of 25 micrograms, 50 micrograms, 75 micrograms or 100 micrograms/day for up to approximately 72 months (mean 2038 days (~5.6 years). The minimum time of exposure to Natpar was 41 days, and the maximum was 2497 days (~6.8 years).

61.2% (30/49) of subjects met the primary efficacy endpoint at end of treatment, defined as albumin-corrected total serum calcium concentration that was normalized or maintained compared to the baseline value and not exceeding the upper limit of normal values; ≥50% reduction from baseline or ≤500 mg of daily calcium supplementation; and ≥50% reduction from baseline or ≤0.25 µg of daily calcitriol supplementation.

The results demonstrate durability of the physiological effects of Natpar over 72 months including maintenance of mean albumin-corrected serum calcium levels (n=49, 2.09 (SD 0.174) mmol/L at baseline; n=38, 2.08 (SD 0.167) mmol/L at 72 months), a decrease in serum phosphate (n=49, 1.56 (SD 0.188) mmol/L at baseline; n=36, 1.26 (SD 0.198) mmol/L at 72 months) and the maintenance of normal calcium phosphate product ($<4.4 mmol^2/L^2$) for all subjects (n=49 at baseline, n=36 at 72 months).

The long-term effects included a decrease in mean urinary calcium excretion to the normal range (n=48, 8.92 (SD 5.009) mmol/day at baseline; n=32, 5.63 (SD 3.207) mmol/day at 72 months), and stabilization of normal mean serum creatinine levels (n=49, 84.7 (SD 18.16) µmol/L at baseline; n=38, 78.2 (SD 18.52) µmol/L at 72 months). In addition, there was maintenance of normal bone mineral density.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Natpar in one or more subsets of the paediatric population in hypoparathyroidism (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of Natpar following subcutaneous administration in the thigh of hypoparathyroidism subjects was consistent with that observed in healthy post-menopausal women who received parathyroid hormone in the thigh and abdomen.

Absorption

Natpar administered subcutaneously had an absolute bioavailability of 53%.

Distribution

Following intravenous administration, Natpar has a volume of distribution of 5.35 L at steady state.

Biotransformation

In vitro and *in vivo* studies demonstrated that the clearance of Natpar is primarily a hepatic process with a lesser role played by the kidneys.

Elimination

In the liver, parathyroid hormone is cleaved by cathepsins. In the kidney, parathyroid hormone and C-terminal fragments are cleared by glomerular filtration.

Pharmacokinetic/pharmacodynamic relationship

Parathyroid hormone (rDNA) was evaluated in an open-label PK/PD study in which 7 patients with hypoparathyroidism received single subcutaneous doses of 50 and 100 micrograms with a 7-day washout interval between doses.

Peak plasma concentrations (mean T_{max}) of Natpar occur within 5 to 30 minutes and a second usually smaller peak at 1 to 2 hours. The apparent terminal half-life ($t_{1/2}$) was 3.02 and 2.83 hours for the 50 and 100 micrograms dose, respectively. The maximum mean increases of serum calcium, which occurred at 12 hours, were approximately 0.125 mmol/L and 0.175 mmol/L with the 50 micrograms and 100 micrograms dose, respectively.

Effect on mineral metabolism

Treatment with Natpar increases serum calcium concentration in hypoparathyroidism patients, and this increase occurs in a dose-related manner. After a single injection of parathyroid hormone (rDNA), the mean serum total calcium reached its peak level between 10 and 12 hours. The calcaemic response is sustained for more than 24 hours after administration.

Urinary calcium excretion

Treatment with Natpar produces a decrease in urinary calcium excretion by 13 and 23% (50 and 100 microgram dose, respectively) to a nadir in the 3 to 6 hour time point, which returns to pre-dosing levels by 16 to 24 hours.

Phosphate

Following injection with Natpar, serum phosphate levels decrease proportionally to PTH(1-84) levels over the first 4 hours and persist over 24 hours post-injection.

Active vitamin D

Serum 1,25-$(OH)_2$D increases following a single dose of Natpar to maximum levels at about 12 hours with a return to near baseline levels by 24 hours. A greater increase in the levels of 1,25-$(OH)_2$D in serum were observed with the 50 micrograms dose than with the 100 micrograms dose, likely due to direct inhibition of the renal 25-hydroxyvitamin D-1-hydroxylase enzyme by serum calcium.

Special populations

Hepatic impairment

A pharmacokinetic study in non-hypoparathyroidism subjects was conducted in 6 men and 6 women with moderate hepatic impairment (Child-Pugh Classification of 7-9 [Grade B]) as compared with a matched group of 12 subjects with normal hepatic function. Following a single 100 micrograms subcutaneous dose, the mean C_{max} and baseline-corrected C_{max} values were 18% to 20% greater in the moderately impaired subjects than in those with normal function. There were no apparent differences in the serum total calcium concentration-time profiles between the 2 hepatic function groups. No dose adjustment for Natpar is recommended in patients with mild to moderate hepatic impairment. There are no data in patients with severe hepatic impairment.

Renal impairment

Pharmacokinetics following a single 100 micrograms subcutaneous dose of Natpar was evaluated in 16 non-impaired subjects (creatinine clearance (CL_{cr}) >80 mL/min) and 16 subjects with renal impairment. The mean maximum concentration (C_{max}) of PTH following 100 micrograms parathyroid hormone (rDNA) in subjects with mild-to-moderate renal impairment (CL_{cr} 30 to 80 mL/min) was approximately 23% higher than that observed in subjects with normal renal function. Exposure to PTH as measured by $AUC_{0\text{-last}}$ and baseline-corrected $AUC_{0\text{-last}}$ was approximately 3.9% and 2.5%, respectively, higher than that observed for subjects with normal renal function.

Based on these results, no dose adjustment is necessary in patients with mild-to-moderate renal impairment (CL_{cr} 30 to 80 mL/min). No studies were conducted in patients on renal dialysis. There are no data in patients with severe renal impairment.

Paediatric population

Pharmacokinetic data in paediatric patients are not available.

Elderly

Clinical studies with Natpar did not include sufficient numbers of subjects aged 65 and over to determine whether response in these subjects is different from younger subjects.

Gender

No clinically relevant gender differences were observed in the REPLACE study.

Weight

No dose adjustment is necessary based on weight.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, mutagenicity, toxicity to fertility and general reproduction, and local tolerance.

Rats treated with daily injections of Natpar for 2 years had dose-dependent exaggerated bone formation and an increased incidence of bone tumours, including osteosarcoma, most probably due to a non-genotoxic mechanism. Due to the differences in bone physiology in rats and humans, the clinical relevance of these findings is unknown. No osteosarcomas have been observed in clinical trials.

Natpar did not adversely affect fertility or early embryonic development in rats, embryo-foetal development in rats and rabbits, or pre/post-natal development in rats. A minimal amount of Natpar is excreted in the milk of lactating rats.

In monkeys receiving daily subcutaneous doses for 6 months, there was an increased occurrence of renal tubular mineralisation at exposure levels 2.7 times the clinical exposure levels at the highest dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Sodium chloride

Mannitol

Citric acid monohydrate

Sodium hydroxide (for pH adjustment)

Solvent

Metacresol

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

Reconstituted solution

After reconstitution, chemical and physical in-use stability of the solution has been demonstrated for up to 14 days when stored in a refrigerator (2°C – 8°C) and for up to 3 days when stored outside the refrigerator not above 25°C during the 14-day use period.

Keep the pen containing a reconstituted cartridge tightly closed in order to protect from light.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Keep the cartridge within its cartridge holder in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

The glass dual-chamber cartridge inside the cartridge holder is made from type I glass with 2 bromobutyl rubber stoppers and a crimp cap (aluminium) with a bromobutyl rubber seal.

Natpar 75 micrograms

Each cartridge in the grey cartridge holder contains 1050 micrograms of parathyroid hormone (rDNA) as powder in the first chamber and 1000 microlitres of solvent in the second chamber (corresponding to 14 doses).

Pack size: Carton containing 2 cartridges.

Carton/cartridge colours are used to indicate the different strengths:

75 micrograms – Grey

6.6 Special precautions for disposal

Parathyroid hormone (rDNA) is injected using the cartridge with a reusable pen. Each pen must be used by only one patient. A new sterile needle must be used for every injection. Use 31 Gx8 mm pen needles. After reconstitution, the liquid must be colourless and practically free of foreign particles; parathyroid hormone (rDNA) must not be used if the reconstituted solution is cloudy, coloured, or contains visible particles.

DO NOT SHAKE during or after reconstitution; shaking may cause denaturation of the active substance.

Read the instructions for use provided in the package leaflet before using the reusable pen.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Takeda Pharmaceuticals International AG Ireland Branch
Block 2 Miesian Plaza
50 – 58 Baggot Street Lower
Dublin 2
D02 HW68
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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/01/2026

10 DATE OF REVISION OF THE TEXT

06/01/2026