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Date 21 December 2020
Subject Advice on a potential candidate for conditional inclusion of rhPTH 1-84 (Natpar®) in chronic hypoparathyroidism (procedure: orphan drugs, conditionals and exceptionals)

Our reference
2020050675

Dear Ms van Ark,

On 23 September 2020, the applicants submitted an application for the conditional inclusion of orphan drugs, conditionals and exceptionals to the National Health Care Institute, for recombinant human parathyroid hormone 1-84 (rhPTH 1-84) (Natpar®). rhPTH 1-84 is registered for use as an additional treatment in adult patients with chronic hypoparathyroidism, whose condition cannot be sufficiently controlled with standard therapy alone. Based on the data in the dossier and the advice of the Scientific Advisory Board (WAR), I would like to inform you that the National Health Care Institute has concluded that treatment with rhPTH 1-84 in this group of patients with hypoparathyroidism meets the criteria for conditional inclusion.

Application for the conditional inclusion of rhPTH 1-84 (Natpar®)
This is an early submission. This means that rhPTH 1-84 has not previously been assessed by the National Health Care Institute. In July 2018, following the submission of a normal preliminary reimbursement dossier, a pre-consultation took place at the National Health Care Institute. During this consultation, it emerged that the study population that was included in the registration studies was not in line with the National Health Care Institute's 'package question[1]'.The registered indication is limited to patients with chronic hypoparathyroidism whose condition cannot be sufficiently controlled with standard therapy. However, in the registration studies carried out for rhPTH 1-84, patients with chronic hypoparathyroidism were included without the requirement that their condition could not be sufficiently controlled with standard therapy. The marketing authorisation holder (MAH) did not subsequently submit a definitive dossier to the National Health Care Institute. The new conditional inclusion of orphan drugs, conditionals and exceptionals started in October 2019. On 23 September 2020, the applicants submitted a conditional inclusion dossier, including a research proposal, to the National Health Care Institute.

Disorder and available effectiveness data

1 1 The question as to whether the medicinal product in question can be included in the basic health care package.

The application that has been submitted refers to rhPTH 1-84 for use as an additional treatment in adult patients with chronic hypoparathyroidism whose condition cannot be sufficiently controlled with standard therapy alone. This is a relatively uncommon disorder. The application that has been submitted concerns approximately 100 patients who are eligible for treatment during the conditional inclusion process.

Hypoparathyroidism is a rare endocrine disorder in which parathyroid hormone (PTH) production is abnormally low or entirely absent. Medical management currently consists of active vitamin D and calcium supplements. This standard treatment has some shortcomings, as it does not involve the physiological replacement of the missing endogenous parathyroid hormone, nor does it facilitate the complete normalisation of calcium and phosphate metabolism. Patients whose condition is insufficiently controlled with such standard therapy experience severe side effects, such as intermittent episodes of muscle cramps, tetanic episodes, and cognitive deficits, which can seriously impact these patients' quality of life. Patients with hypoparathyroidism who are receiving the standard treatment are also at risk of long-term extraosseous calcifications, especially in the kidneys, brain, and lenses of the eyes.

rhPTH 1-84 is completely identical to human PTH, which consists of 84 amino acids. Thus, rhPTH 1-84 replaces the missing hormone in patients with chronic hypoparathyroidism. In a large proportion of the approx. 4,250 hypoparathyroidism patients in which the standard treatment produced partial correction, their condition was sufficiently controlled. However, this result was not observed in some patients (approx. 100). Based on the results of previous studies, there is evidence that rhPTH can lead to improved calcium-phosphate homeostasis. At the present time, there is no other treatment that can influence the disease in this group of patients with chronic hypoparathyroidism whose condition cannot be sufficiently controlled with standard therapy alone.

Research proposal
The intended aim of the additional treatment with rhPTH 1-84 is to alleviate the symptoms of hypocalcaemia and hypercalcaemia (and, as a result, reduce hospitalisations and visits to accident and emergency departments prompted by these symptoms), as well as an improvement in quality of life, a better employment rate, and the prevention of long-term complications, such as renal insufficiency (because a lower dose of calcium supplements and active vitamin D can be achieved).

The applicants have submitted a research proposal for conditional inclusion, based on an ongoing international study, the 401 study. The patients who are eligible for participation in this RCT are those in whom chronic hypoparathyroidism and hypoparathyroidism-related symptoms were diagnosed at least 12 months previously, and who have been treated with active vitamin D, possibly in combination with calcium supplements, for at least four months. The study population in the 401 study matches the target population for reimbursement. At the present time, a sufficient number of Dutch patients have been included in this ongoing study.

The procedure for the conditional inclusion of orphan drugs, *conditionals* and *exceptionals* indicates that entitlement to conditionally included care is linked to

National Health Care Institute
Care

Date
21 December 2020

Our reference
2020050675

the requirement to participate in a study. This means that patients are only entitled to reimbursement for care if they participate in the study into its effectiveness (or cost effectiveness). Thus, a register (monitor) is being established for any Dutch patients who cannot participate in the 401 study (or who are no longer able to do so).

Assessment and conclusions of the National Health Care Institute
Based on the data in the dossier and on the advice of the WAR, the National Health Care Institute concludes that treatment with rhPTH 1-84 for use as an additional treatment in adult patients with chronic hypoparathyroidism whose condition cannot be sufficiently controlled with standard therapy alone meets the criteria for conditional inclusion[2], namely:

- rhPTH 1-84 has been granted marketing authorisation by the EMA and has 'orphan drug' and 'conditional' status;
- This is a case of an unmet medical need;
- The marketing authorisation holder is the dossier's lead applicant. The co-applicants are an independent research institute, treating physicians, and patient associations;
- Based on the data it has collected, this study is expected to provide an answer to the 'package question';
- The National Health Care Institute anticipates that the 'package question' will be answered within three and a half to four years.

Advice from National Health Care Institute
Based on these conclusions, we recommend that rhPTH 1-84 be designated as a potential candidate for conditional inclusion.

Phase 2 of the procedure will commence when you adopt this advice. We ask the parties to formulate their plans in greater detail and to draw up a covenant setting out the agreements needed to ensure that the CI process is conducted carefully and successfully. The Ministry of Health, Welfare and Sport will have to conclude a financial arrangement with the marketing authorisation holder. On the completion of phase 2 (at which point a covenant will have been drawn up and a financial arrangement concluded), we will send you a follow-up advice, on which you can base your final decision regarding the inclusion of rhPTH 1-84 in the conditional inclusion.

Yours sincerely,

Tiana van Grinsven
Acting Chair of the Executive Board

cc The applicants (or co-applicants) who submitted the research proposal

[2] an overview of the criteria for CI can be found in the most recent version of the letter on the conditional inclusion procedure for orphan drugs, conditionals, and exceptionals. This letter can be found at our website, at: https://www.zorginstituutnederland.nl/werkagenda/voorwaardelijke-toelating-weesgeneesmiddelen-conditionals-en-exceptionals

National Health Care Institute
Care

Date
21 December 2020

Our reference
2020050675

Annex 1. Price and dose of rhPTH 1-84 (Natpar®)

The pharmacy purchase price (AIP) of one pack of Natpar® 25, 50, 75 or 100 mcg per dose of powder and per solution for injection is €5,638.36 (flat pricing). One pack of Natpar® consists of two cartridges, each containing 14 doses.[3]

Natpar® should be administered once a day by subcutaneous injection into the thigh.
After completing a training session, patients can self-administer this injection.[4] The marketing authorisation holder has indicated that they will make the pen injector available to patients.

One pack of Natpar® is sufficient for a 28-day period of treatment. Thus, patients will require 13 packs per year. This brings the cost, per patient per year, to 13 x €5,638.36 = €73,298.68.

No further account is taken of the excess and/or personal contributions here, and patient compliance is assumed to be 100%. Table 1 contains an overview of the costs per patient per year.

Table 1: Costs per patient for the use of Natpar® with chronic hypoparathyroidism

	Natpar®
Daily dose	One injection (25, 50, 75 or 100 mcg)
Purchase price per pack of 28 doses (AIP)	€5,638.36 (same for 25, 50, 75 or 100 mcg)
Number of packs required per year	13
Total annual cost	€73,298.68

[3] Z-index November 2020

[4] SmPC rhPTH 1-84 (Natpar®) 2019