NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Palopegteriparatide for treating chronic hypoparathyroidism

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using palopegteriparatide in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: October 2025

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using palopegteriparatide in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 21 November 2025
- Second evaluation committee meeting: 10 February 2026
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Palopegteriparatide should not be used to treat chronic hypoparathyroidism in adults.

1.2 This recommendation is not intended to affect treatment with palopegteriparatide that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Palopegteriparatide is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because there is not enough evidence to determine whether palopegteriparatide is value for money in this population.

Why the committee made these recommendations

Usual treatment for chronic hypoparathyroidism is calcium and vitamin D supplements. Some people also have thiazide diuretics.

Results from a clinical trial comparing palopegteriparatide plus usual treatment with placebo plus usual treatment are uncertain. This is because the trial design may not allow a fair comparison, for reasons including:

- usual treatment in the trial may not be the same as usual treatment in the NHS
- the way that the trial measured how well the treatments work may not show whether palopegteriparatide plus usual treatment works better than usual treatment alone.

There are also uncertainties with the economic model including its design and the evidence used to inform it.

Because of the uncertainties in the clinical evidence and the economic model, it is not possible to determine the most likely cost-effectiveness estimates for palopegteriparatide. Further analyses are needed. So, palopegteriparatide should not be used.

2 Information about palopegteriparatide

Marketing authorisation indication

2.1 Palopegteriparatide (Yorvipath, Ascendis Pharma) is 'a parathyroid hormone (PTH) replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for palopegteriparatide.

Price

2.3 The list price is £7,406.00 per pack of 2 pre-filled multiuse disposable injection pens (excluding VAT; BNF online accessed October 2025). Pens are available in different doses.

2.4 The company has a commercial arrangement, which would have applied if palopegteriparatide had been recommended.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Ascendis Pharma will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Ascendis Pharma, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

3.1 Chronic hypoparathyroidism is an endocrine condition caused by insufficient parathyroid hormone (PTH). PTH is produced by the parathyroid glands in the neck. For about 75% of people with chronic hypoparathyroidism, their condition was caused when the parathyroid glands were removed or accidentally damaged during surgery. The remaining 25% of chronic hypoparathyroidism has non-surgical causes, and may be related to autoimmunity, or may be genetic or idiopathic. PTH, alongside vitamin D, is a key regulator of calcium and phosphate homeostasis. In chronic hypoparathyroidism, insufficient PTH disrupts this homeostasis, leading to persistent low levels of calcium in the blood (hypocalcaemia). The patient experts explained that living with chronic hypoparathyroidism is a constant and lifelong challenge to maintain calcium levels and avoid symptoms, which can often be unpredictable. They noted that the most frequent symptoms of chronic hypoparathyroidism include fatigue, confusion, tingling or numbness, bone pain and anxiety. The clinical experts explained that chronic hypoparathyroidism is also associated with several long-term complications, including kidney and cardiovascular disease. The patient experts described how chronic hypoparathyroidism can have a substantial impact on quality of life, with many people reporting reduced ability to sleep, work and socialise. They highlighted that people with chronic hypoparathyroidism often need assistance from carers. This caring responsibility often falls to family members and can cause significant emotional and physical strain. The committee concluded that chronic hypoparathyroidism can have a considerable impact on people with the condition and their carers.

Clinical management

Treatment options and positioning of palopegteriparatide

3.2 The clinical experts explained that the goals of treatment for people with chronic hypoparathyroidism include:

- maintaining serum calcium in the lower part of the normal range
- reducing symptoms associated with chronic hypoparathyroidism
- improving quality of life.

They noted that there are no UK-specific guidelines for treating chronic hypoparathyroidism and that NHS healthcare professionals follow European and international guidelines. The company cited several guidelines, but clarified that the guidelines from the 'Second International Workshop' (Khan et al. 2022) were the most relevant for this evaluation because these were the most recently published. These guidelines recommend that chronic hypoparathyroidism is first treated with calcium and vitamin D supplements (referred to as 'standard treatment' from here on). The guidelines also recommend considering PTH replacement treatment (such as palopegteriparatide) for chronic hypoparathyroidism that is not adequately controlled (NAC) on standard treatment. The Second International Workshop 2022 guidelines define NAC chronic hypoparathyroidism as any of the following:

- symptomatic hypocalcaemia
- hyperphosphataemia (high levels of phosphate in the blood)
- renal insufficiency
- hypercalciuria (high levels of calcium in the urine)
- poor quality of life.

The company noted that the Second International Workshop 2022 guidelines also state that people needing 2,000 mg or more of calcium per day may benefit from PTH replacement treatment. The company

asked the committee to evaluate palopegteriparatide for the subpopulation of people with NAC chronic hypoparathyroidism. This is a smaller population than the licensed population (see section 2.1). The company estimated that, in 10% to 20% of people with chronic hypoparathyroidism in the NHS, the condition would be defined as NAC using the criteria in the Second International Workshop 2022 guidelines. The EAG agreed with restricting the population to people with NAC chronic hypoparathyroidism. But it noted that there is no consistent definition of NAC chronic hypoparathyroidism in the literature, and it was unclear how it would be defined in the NHS. The EAG had received clinical advice that suggested that people could meet any of the Second International Workshop 2022 guidelines criteria but still have well-controlled chronic hypoparathyroidism and palopegteriparatide would not necessarily be suitable for them. The EAG also emphasised that the population for whom palopegteriparatide is suitable would be a small proportion of the total chronic hypoparathyroidism population. In response, the clinical experts at the meeting noted that they thought the Second International Workshop 2022 guidelines criteria would be broadly reflective of the criteria used in the NHS to determine palopegteriparatide suitability. They said that in clinical practice palopegteriparatide would most likely be offered to people who:

- had a poor quality of life because of their hypoparathyroidism, or
- had high rates of hospitalisations or testing requirements, or
- were at risk of complications, such as people with hypercalciuria.

The clinical experts also thought that people who need 2,000 mg of calcium per day would likely have another indicator of NAC chronic hypoparathyroidism. Specifically, the clinical experts explained that having a high dose of calcium supplementation can lead to hypercalciuria, and they noted that it is the hypercalciuria that carries a risk of complications. The committee concluded that there is no

consistent definition of inadequate control used in NHS practice, or in European or international guidelines for chronic hypoparathyroidism. But it was satisfied that the criteria suggested by the company based on the Second International Workshop 2022 guidelines would be appropriate for determining eligibility for palopegteriparatide and broadly aligned with how clinical experts would use it in clinical practice.

Unmet need in people with NAC chronic hypoparathyroidism

3.3 The patient experts explained that, in the absence of a PTH replacement treatment like palopegteriparatide, people who have NAC chronic hypoparathyroidism experience significant and unpredictable fluctuations in calcium levels and related symptoms. These can have a major impact on their physical and mental wellbeing. One patient expert explained that fluctuations in calcium levels and symptoms can be worse in the first year after diagnosis and can increase the need for emergency visits to hospital. But they also explained that people with chronic hypoparathyroidism try to avoid emergency care because the condition is challenging to manage and the care provided is generally poor. The patient experts noted that long-term exposure to standard treatment with calcium and vitamin D supplementation can result in an increased risk of renal complications. In addition, standard treatment does not treat hyperphosphataemia, and this must be managed by dietary changes. The patient experts thought that palopegteriparatide would help to stabilise their calcium levels, allow them to take reduced doses of standard treatment and decrease the risk of long-term complications. They provided feedback from 1 person with chronic hypoparathyroidism who had been able to have palopegteriparatide over the past year and who described the treatment as “life-changing”. The committee concluded that people with chronic hypoparathyroidism that is NAC on standard treatment would highly value additional treatment options.

Clinical effectiveness

Data source

3.4 The clinical-effectiveness evidence for palopegteriparatide came from the PaTHway trial. This was a 26-week, phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial followed by a 156-week open-label extension. PaTHway was done in 21 sites across 7 countries, but did not include any sites in the UK. At the start of the double-blind phase, 63 people with chronic hypoparathyroidism were randomised to palopegteriparatide with standard treatment and 21 were randomised to placebo with standard treatment. A total of 79 people completed the double-blind phase and entered the open-label extension. The committee concluded that evidence from PaTHway was relevant for determining the clinical benefit of palopegteriparatide, but noted that there were several uncertainties (see sections 3.5 to 3.8).

Population

3.5 People in PaTHway did not need to have NAC chronic hypoparathyroidism to enter the trial, but the company noted that most people did. The exact proportion is considered confidential by the company and cannot be reported here. But the EAG questioned whether the population in the trial was generalisable to the population expected to have palopegteriparatide in the NHS. The clinical experts explained that the trial population was generalisable to the NHS, but that the proportion of people in the trial with symptomatic hypocalcaemia was lower than would be expected. The EAG thought that this was likely because of the trial inclusion criteria, which needed people to be on stable standard-treatment doses for at least 5 weeks before the start of the trial. The committee concluded that the trial population was broadly generalisable to the NHS. But the committee said that because the trial population did not need to meet the NAC criteria, there would likely be some differences between it and the population that would have palopegteriparatide in NHS

clinical practice. The committee concluded that it would take this uncertainty into account in its decision making.

Standard treatment

3.6 The trial protocol specified that people in both arms had to reduce their vitamin D dose by one-third to one-half at the start of the trial. Subsequent dose decreases or discontinuations followed a predefined algorithm. The company stated that this decrease in vitamin D dose was needed to assess whether people could become independent from standard treatment. The EAG also explained that, while the calcium dose could vary during the trial, an aim of the trial was for people to reduce therapeutic calcium to meet the primary outcome (see section 3.7). Furthermore, the EAG noted that thiazide diuretics were not permitted in the trial because of their potential to have a confounding effect on urinary calcium. The EAG cited clinical advice that suggested that thiazide diuretics would be offered to many people with NAC chronic hypoparathyroidism in the NHS. Thiazide diuretics are also recommended in the Second International Workshop 2022 guidelines to treat hypercalciuria in people with chronic hypoparathyroidism. The EAG summarised that standard treatment was suboptimal in PaTHway because the doses of calcium and vitamin D were reduced and thiazide diuretics were prohibited. It noted that this may have biased the assessment of comparative effectiveness. The clinical experts agreed that thiazide diuretics have an important role in treating hypercalciuria, but cautioned that they are only used by a small proportion of people and are associated with several side effects. The committee concluded that the trial design likely meant that standard treatment in the trial was not as effective as standard treatment in the NHS. It concluded that this contributed to the substantial uncertainty around the effectiveness of palopegteriparatide compared to standard treatment. To support decision making, the committee asked the company to explore adjustments to the efficacy data for the standard-treatment arm of PaTHway so that it better reflects standard treatment in the NHS. The committee said that this

should include adjustment to reflect the expected benefit of thiazide diuretics. It said that these adjustments should be informed by alternative evidence sources for the effectiveness of standard treatment in the NHS if available, or clinical expert opinion.

In addition, the committee noted that using an alternative evidence source for the effectiveness of standard treatment to inform an indirect comparison with palopegteriparatide could help to reduce some of the uncertainty. But it said that this was not essential to support its decision making and that it may be associated with further uncertainty.

Primary outcome

3.7 The primary outcome of PaTHway was a composite outcome at week 26 in which all of the following criteria had to be met:

- albumin-adjusted serum calcium within normal range
- independence from therapeutic doses of calcium (600 mg or more per day)
- independence from active vitamin D
- no increase in trial drug within weeks 22 to 26.

At week 26, a statistically significantly greater proportion of people in the palopegteriparatide arm met the primary outcome than in the standard-treatment arm (78.7% versus 4.8%, $p<0.0001$). A numerically higher proportion of people in the palopegteriparatide arm met each individual criterion than in the standard-treatment arm:

- albumin-adjusted serum calcium within normal range: 80.3% versus 47.6%
- independence from therapeutic doses of calcium: 93.4% versus 4.8%
- independence from active vitamin D: 98.4% versus 23.8%
- no increase in trial drug within weeks 22 to 26: 93.4% versus 57.1%.

The EAG was concerned that the design of the primary outcome did

not allow a fair comparison between palopegteriparatide and standard treatment. This was because the EAG reasoned that becoming independent from standard treatment (therapeutic doses of calcium and vitamin D) was not a plausible goal of standard treatment. Instead, the EAG thought that the primary outcome was designed to show that palopegteriparatide could be an effective PTH replacement therapy, but that it did not show that palopegteriparatide was more clinically effective than standard treatment. The company explained that the primary outcome was designed in collaboration with regulators and that the independence-from-standard-treatment components were useful to assess the benefit of palopegteriparatide for restoring physiological PTH function. The EAG also highlighted that the primary outcome was a surrogate outcome; that is, it did not directly measure clinical benefit. It said that the primary outcome may predict clinical benefit, because:

- better calcium control might be expected to result in better symptom control and better quality of life
- lower standard-treatment use might be expected to result in fewer long-term complications and less healthcare resource use.

But the EAG noted that the primary outcome provided no evidence of this. The company noted that quality-of-life outcomes were measured in PaTHway and did show a benefit for palopegteriparatide. But it noted that the short timeframe of the trial meant that the benefits related to long-term complications did not have time to emerge. In addition, the company explained that palopegteriparatide is expected to reduce resource use and hospitalisations, but that this benefit would be more likely to be observed in real-world practice than in the trial. They said that this was because people in the trial were more intensively monitored than would be expected in real-world practice. They said that this extra monitoring would have prevented many events that would have led to healthcare resource use. The patient and clinical experts agreed that outcomes focused on direct clinical benefit would have

been valuable in PaTHway. The patient experts further described that they would place the most value on having fewer calcium fluctuations and symptoms, fewer complications, fewer hospitalisations, and a better quality of life. The committee concluded that the primary outcome did not capture aspects of treatment that are important to people with the condition. It also said that the primary outcome suggested that palopegteriparatide was an effective PTH replacement treatment. But it concluded that there was substantial uncertainty about whether the primary outcome could be used to assess whether there was any clinical benefit of palopegteriparatide over standard treatment. The committee agreed that it was unlikely that people in the standard-treatment arm would be able to meet the 'independence from therapeutic doses of calcium' component of the primary outcome. Furthermore, the committee recalled that high calcium doses were only a surrogate for hypercalciuria (see section 3.2). To support its decision making, the committee asked the company to provide an analysis of the clinical-effectiveness results from PaTHway excluding the 'independence from therapeutic doses of calcium' component of the primary outcome.

Patient-reported outcomes

3.8 Patient-reported outcomes were assessed in PaTHway using the generic 36-item Short Form Survey (SF-36) and EuroQol 5-dimension (EQ-5D) questionnaires and the disease-specific Hypoparathyroidism Patient Experience Scale (HPES). People on palopegteriparatide reported better health-related quality of life than people on standard treatment. But the EAG recalled that the treatment algorithm used in PaTHway attempted to reduce the dose of standard treatment used (see section 3.6). People on palopegteriparatide greatly reduced their daily average calcium dose by week 6, and had largely discontinued vitamin D by week 4. In contrast, people in the standard-treatment arm remained on high calcium doses throughout the 26-week period. Vitamin D doses decreased in the standard-treatment arm after the protocol-mandated reduction (see

section 3.6), but remained higher than in the palopegteriparatide arm at all timepoints. The EAG thought that this difference in the amount of standard-treatment use could lead to 'functional unblinding', in which people know what treatment they are on, and noted that this could have led to larger than expected differences in patient-reported outcomes. The company acknowledged that while functional unblinding may have occurred, it thought that this would have had minimal impact on the patient-reported outcomes. The committee concluded that there was likely some functional unblinding in PaTHway and that this will have affected assessment of the patient-reported outcomes, but that the magnitude of this was uncertain. The committee agreed to take this uncertainty into account in its decision making.

Economic modelling

Company's modelling approach

3.9 The company presented a 3-state on-or-off-treatment model to compare the cost effectiveness of palopegteriparatide with standard treatment. The 3 mutually exclusive health states were adequately controlled (AC; or 'on' palopegteriparatide), NAC (or 'off' palopegteriparatide), and death. People entered the model in the AC health state if starting palopegteriparatide or in the NAC health state if starting standard treatment. People in the model could move from AC to NAC when stopping treatment with palopegteriparatide, but could not move from NAC to AC. The EAG had serious concerns about the model structure. It noted that the model used an approach in which health states were defined by the treatment used rather than a clinical outcome. It thought that this represented a conceptually weak foundation because it decoupled the model structure from the underlying pathophysiology of chronic hypoparathyroidism.

The EAG also highlighted that a key model assumption was that everyone on palopegteriparatide was assumed to be in the AC health state, whereas everyone on standard treatment was assumed to be in the NAC

health state. The EAG highlighted that this assumption meant that the AC and NAC definitions used to define the health states were different from those used to generate several model inputs (see section 3.10). Specifically, the health-state definitions were based on allocation to palopegteriparatide or standard treatment and the definitions used to generate model inputs were based on resource use. This assumption was important because the NAC health state was associated with worse outcomes, including lower utility values, and higher complication rates, adverse-event rates, mortality, and healthcare resource use. The company explained that this was a simplifying assumption, given that a high proportion of people in PaTHway met the primary outcome of biochemical control and independence from standard treatment. The company said that people having standard treatment were classified as NAC in the model because it reflected the target population (NAC on standard treatment) and the proposed positioning of palopegteriparatide. The EAG questioned whether this assumption was appropriate. It highlighted that only 78.7% of people met the primary outcome in the palopegteriparatide arm. It also highlighted that the design of the PaTHway primary outcome meant that few people having standard treatment would be expected to meet it (see section 3.7). Yet, the EAG noted that 1 person (4.8%) in the standard-treatment arm did meet the primary outcome. Clinical advice to the EAG suggested that some people with chronic hypoparathyroidism can have good calcium control with standard treatment, and can taper their treatment with the long-term aim of achieving independence. But the model does not allow people on standard treatment to move to the AC health state. In response, the company explained that spontaneous recovery on standard treatment is not typically seen in people with chronic hypoparathyroidism.

The committee shared the EAG's concerns that the model structure was flawed. But the committee also recognised that the limitations of the clinical evidence meant that the company had few modelling options. The

committee thought that it was appropriate to base the health states on AC and NAC. But the committee thought that allocation to palopegteriparatide was not an appropriate proxy for AC, and allocation to standard treatment was not an appropriate proxy for NAC. The EAG suggested that a viable alternative would be to use the PaTHway primary outcome as a measure of treatment response and to define the AC and NAC health states based on whether people met this. The EAG noted that the benefit of a response-based model was that it would link modelled treatment response to clinically relevant outcomes, namely biochemical control and independence from standard treatment. It also noted that a response-based model would allow inclusion of an assessment period of, for example, 6 months. It said that during this assessment period treatment response could be evaluated and people whose condition did not respond to treatment would stop. The company disputed this, explaining that the on-or-off model better reflects real-world clinical practice, and a response-based model would underestimate the benefits of palopegteriparatide. The company also highlighted that a response-based model would include a stopping rule for non-responders and that this would limit palopegteriparatide costs. So the company claimed that the cost effectiveness of palopegteriparatide would not differ greatly between the 2 modelling approaches. But the committee agreed that a response-based model would be more suitable for decision making and might reduce some uncertainty in the model. So, to support its decision making, the committee asked the company to provide a response-based model with treatment response based on the primary outcome of PaTHway. The committee recalled its discussions in section 3.7 about the design of the primary outcome and how few people on standard treatment would be expected to meet it. So, to support its decision making, the committee also asked the company to provide a scenario in which the ‘independence from therapeutic doses of calcium’ component was excluded from the primary outcome and from the health-state definition.

Additional data sources for model inputs

3.10 The company used evidence from PaTHway to determine inputs for utility values and adverse-event rates. The company used other evidence sources to inform other model inputs. Mainly, the company used an analysis of the Clinical Practice Research Datalink (CPRD) Aurum database. The CPRD Aurum database covers participating primary care practices in the UK and links with Hospital Episode Statistics and Death Registration data from the Office for National Statistics. The company was able to identify people with chronic hypoparathyroidism in the CPRD. But the CPRD does not contain direct clinical measures such as serum calcium levels or treatment dosing. So, control of the condition was inferred from patterns of NHS activity and verified by clinical opinion. The company used the following definitions to differentiate between AC and NAC chronic hypoparathyroidism:

- AC: 5 or fewer outpatient visits and less than 1 inpatient visit per patient per year
- NAC: more than 5 outpatient visits and 1 or more inpatient visit per patient per year.

The company then compared these people with matched controls to produce estimates for the additional mortality risk and complication risk compared with the general population. Similarly, the company applied these definitions to people with chronic hypoparathyroidism to estimate the healthcare costs associated with being in each health state. The EAG's primary concern was that none of the modelled benefits of palopegteriparatide, except for utility values and adverse-event rates, were supported by evidence from PaTHway. Instead, these benefits were derived through a chain of assumptions that linked treatment allocation with outcomes, with little supporting evidence that such a surrogate relationship exists. The EAG again highlighted that the AC and NAC definitions used in the CPRD analysis were different from the AC and NAC definitions used to define the model health states. The

former was based on resource use and the latter on allocation to palopegteriparatide or standard treatment. The committee noted that the resource-use definitions that informed the AC and NAC health states in the CPRD analysis were not exhaustive. For instance, they would not capture people who had both 5 or fewer outpatient visits and 1 or more inpatient visit per year. The committee asked the patient experts how the resource-use definitions related to patient experience. The patient experts explained that they would struggle to meet the company's NAC criteria, despite feeling that their condition is poorly controlled, because hypoparathyroidism is often managed in primary care. They reiterated that people with poorly controlled hypoparathyroidism may avoid seeking emergency care (see section 3.3) and would not necessarily have any inpatient admissions over the course of a year. The committee considered that the CPRD could be a reasonable source for these estimates. But it thought that the company's definitions of AC and NAC based on resource use were problematic and did not reflect patient experience. It also agreed with the EAG that the definitions of AC and NAC were not sufficiently supported by empirical evidence. The committee recognised that the rarity of chronic hypoparathyroidism meant that evidence to support the assumed surrogate relationships may not be available. But the committee wanted to ensure that the definitions of AC or NAC used to generate these inputs reflected the updated definitions used to define the model health states. That is, they should ideally be based on clinically relevant outcomes such as control of the condition. The committee said that this may involve using more data from PaTHway and literature sources, and robust, transparent clinical expert opinion to inform the model inputs. Further discussion on this is presented in the following sections.

Modelling of mortality

3.11 The CPRD analysis estimated that people with chronic hypoparathyroidism would have substantially higher mortality compared

with the general population. The exact results are considered confidential by the company and cannot be reported here. The analysis also suggested that people with NAC chronic hypoparathyroidism would have higher mortality than people with AC chronic hypoparathyroidism. The company applied the excess mortality calculated from the CPRD to the AC ('on' palopegteriparatide) and NAC ('off' palopegteriparatide) health states in the model. This meant that the company modelled a benefit of palopegteriparatide in reducing mortality compared with standard treatment. Although the EAG accepted that palopegteriparatide could reduce excess mortality in people with chronic hypoparathyroidism, it noted that there was no evidence from PaTHway to support this. It also noted that there was no clear justification for assuming that any mortality benefit of palopegteriparatide would reflect the differences in mortality between high- and low-resource-use groups used in the CPRD. Additionally, the EAG explained that the calculated excess mortality risk of chronic hypoparathyroidism versus the general population was higher than estimates from the literature, including an estimate from a previous analysis of CPRD data sponsored by the company. The clinical experts stated that palopegteriparatide may increase length of life but more data is needed. The committee concluded that the relationship between palopegteriparatide treatment and reduced mortality had been inadequately justified by the company. To reduce uncertainty, the committee asked the company to:

- Consider doing scenario analyses using estimates of mortality risk from the literature.
- Explore the evidence for surrogate relationships between the trial outcomes and mortality. The committee said that the company should provide evidence supporting the outcome relationship together with an explanation of how the relationship is quantified for use in modelling. The committee noted that section 4.6.5 onwards in NICE's manual on health technology evaluations provides important information on justifying surrogate relationships.

- Provide updated estimates of mortality from the CPRD analysis, ensuring that definitions of AC or NAC used to generate these inputs reflect the updated definitions used to define the model health states. That is, they should be based on clinically relevant outcomes such as control of the condition.

Modelling of complications

3.12 Complications in the model were captured by a linked event-based sub-model. Using a targeted literature review and clinical input, the company identified relevant complications, which included chronic kidney disease and cardiovascular disease. Then, the company estimated incidence rates for each complication using the CPRD, and compared the rates for chronic hypoparathyroidism (splitting out AC and NAC) with matched controls. The analysis suggested that people with NAC chronic hypoparathyroidism have higher risks of all modelled complications than people with AC chronic hypoparathyroidism. When applied to the model, this translated to a benefit of palopegteriparatide in reducing the risk of all complications. The EAG thought that it was plausible that palopegteriparatide could reduce the risk of complications compared with standard treatment. But it highlighted the lack of evidence to support this. The committee concluded that the relationship between palopegteriparatide treatment and reduced incidence of complications had been inadequately justified by the company. To reduce uncertainty, the committee asked the company to:

- Consider doing scenario analyses using estimates of complication risk from the literature.
- Explore the evidence for surrogate relationships between the trial outcomes and complications. The committee said that the company should provide evidence supporting the outcome relationship together with an explanation of how the relationship is quantified for use in modelling. The committee noted that section 4.6.5 onwards in NICE's

manual on health technology evaluations provides important information on justifying surrogate relationships.

- Provide updated estimates of complication risk from the CPRD analysis, ensuring that definitions of AC or NAC used to generate these inputs reflect the updated definitions used to define the model health states. That is, they should be based on clinically relevant outcomes such as control of the condition.

Modelling of adverse-event rates

3.13 Hypocalcaemia and hypercalcaemia were modelled separately as treatment-related adverse events, based on exposure-adjusted rates from PaTHway. The company used any grade of adverse event to calculate the model rates. This meant that the company applied adverse-event treatment costs for all hypocalcaemia and hypercalcaemia events irrespective of severity. The company's rationale for this was that people in the trial were more intensively monitored than people would be in the NHS. So, with less-intensive monitoring in real-world clinical practice, lower-grade adverse events would be more likely to become more severe and need hospital treatment. The EAG thought that the adverse-event rates should be calculated using only those adverse events that resulted in urgent care visits or hospitalisation. The EAG noted that the company's cost for adverse events (see section 3.16) assumed hospitalisation. So, it considered that the company's argument implied that all adverse events, even the least severe, would escalate to a level needing hospitalisation. The EAG thought that this was implausible. To support its decision making, the committee asked the company to provide evidence that the risk of adverse events would be higher in clinical practice than in PaTHway.

Utility values

3.14 The company calculated utility values using EQ-5D data collected in PaTHway. It used an analysis of covariance (ANCOVA) model that excluded data collected at interim visits. The company chose this

approach because it thought that the treatment effect of palopegteriparatide was not fully realised for everyone at the interim visits. The EAG questioned this and noted that the palopegteriparatide EQ-5D data showed a large and sustained increase from baseline at the week-10 visit. So, the EAG thought that a mixed model for repeated measures (MMRM) would be more appropriate to analyse the data, because an MMRM can include data from interim visits. The committee agreed with the EAG that the MMRM approach is the standard method for analysing longitudinal utility data with repeated measurements because it makes use of all available data. So, the committee concluded that the MMRM approach should be used. It also concluded that the utility values should be based on the revised health states for AC and NAC defined by response to treatment rather than treatment used (see section 3.9).

Costs

Healthcare resource use

3.15 The company calculated maintenance costs associated with AC and NAC chronic hypoparathyroidism by applying the resource-use definitions to people in the CPRD (see section 3.10). The company then applied these costs to the AC and NAC health states in the model. These costs were applied for every cycle that people remained in that health state. The cost applied to the NAC health state was substantially higher than the cost applied to the AC health state. So, the model predicted that palopegteriparatide would generate large cost savings (the exact costs used are considered confidential by the company and cannot be reported here). The EAG had major concerns about these costs. It noted that these costs were derived through circular reasoning. This is because resource use was used to stratify people in the CPRD as either AC or NAC and then this stratification was used to infer a relationship between resource use and disease severity. The EAG also noted that the CPRD data captures resource use unrelated to chronic hypoparathyroidism, such as hospitalisations because of comorbid conditions, and so does not align

with the NICE reference case. Moreover, the EAG highlighted that the CPRD cohort mostly consisted of chronic hypoparathyroidism with a non-surgical aetiology. In contrast, in the NHS, most chronic hypoparathyroidism is post-surgical. The EAG reasoned that people with non-surgical hypoparathyroidism and people with post-surgical hypoparathyroidism would have different resource-use needs (and costs). So, the EAG presented a scenario that reweighted the CPRD analysis to align with the non-surgical and post-surgical mix in PaTHway. The committee recalled its earlier conclusion that the resource-use definitions used in the CPRD analysis to differentiate the AC and NAC health states were not appropriate. So, it concluded that the costs generated from the CPRD analysis were not reliable and that the company needs to provide more robust model inputs. To assist with its decision making, the committee also requested that the company provide a scenario in which resource-use costs are based on resource use in PaTHway, but recognised the limitations associated with this. The committee thought that this would have the additional benefit of removing the need for separate adverse-event costs applied in the model.

Adverse-event costs

3.16 Hypocalcaemia and hypercalcaemia were modelled separately as treatment-related adverse events, based on exposure-adjusted rates from PaTHway. The company then applied the NHS reference cost from 2010 to 2011 for ‘Hospitalisation for Heart Failure’. This was inflated to 2025 cost of £3,315. The EAG highlighted that the company’s approach to modelling adverse-event rates was such that this cost would be applied to each hypocalcaemia and hypercalcaemia adverse event, irrespective of severity or whether it needed a hospital admission (see section 3.13). The EAG also considered that a cost for heart failure would not be an accurate reflection of the cost of managing hypocalcaemia or hypercalcaemia. So, the EAG instead preferred the NHS reference cost for ‘Fluid and Electrolyte Disorders’, assuming a non-elective short-stay admission. This cost was £564. The clinical experts noted that while these adverse events

can usually be treated on the same day, there can be variation in the time spent in hospital because of complications or the need for observation. The patient experts agreed that time in hospital can vary. But they also reminded the committee that people with chronic hypoparathyroidism are keen to avoid emergency care as much as possible (see section 3.3). So, many would choose day-case treatment rather than risk a prolonged hospital stay. The company also provided a scenario analysis with a cost calculated from the CPRD. This cost was higher than the estimate provided by the EAG but lower than the initial estimate provided by the company. The company considered the exact value to be confidential and so it cannot be reported here. This scenario was provided after the EAG report and so was not critiqued by the EAG. The committee was uncertain about what the appropriate cost would be for these adverse events. It thought that, in the absence of a specific NHS reference cost, using a cost derived from the CPRD could be useful. But it would need EAG assessment to confirm whether this cost had been appropriately calculated and that it did not capture costs outside of the NICE reference case. To reduce uncertainty, the committee also requested that the company:

- provide the most recently published value of the 'Hospitalisation for Heart Failure' NHS reference cost
- consider how the resource use for hypocalcaemia and hypercalcaemia might differ from the resource use associated with 'Hospitalisation for Heart Failure' and 'Fluid and Electrolyte Disorders'
- seek further clinical input on the:
  - typical length of stay needed to treat these adverse events
  - typical cost of such treatment episodes
  - variation in length of stay and cost.

Drug wastage

3.17 The company did not include drug wastage in its model. The EAG highlighted that people have palopegteriparatide dose modifications

throughout treatment. When these dose changes exceed the minimum or maximum dose deliverable by their current pen, people must switch to a new pen size. The EAG thought that this would imply wastage of unused pens, and so it applied half-a-pack wastage when people moved between pen sizes. The company had also applied a relative dose intensity (RDI) reduction to palopegteriparatide acquisition costs equal to the adherence rate in PaTHway. The EAG explained that because the pens have a 14-day expiry, it was implausible that dose reductions or skipped doses would lead to lower costs. So, it set the RDI to 100%. The company acknowledged that setting the RDI to 100% was appropriate. It also acknowledged that there was uncertainty around the assumption of drug wastage. The committee concluded that the EAG's approach to wastage and RDI was appropriate.

Administration costs

3.18 Palopegteriparatide is administered as a once-daily subcutaneous injection. The EAG had received clinical advice that some people, such as people with disabilities or older people, would need assistance with administration. So, the EAG included an administration cost equal to a daily nurse visit for 10% of people on palopegteriparatide. In response, the clinical experts explained that they would expect the need for nurse visits to decrease. They explained that the people who may be unable to self-administer palopegteriparatide would likely already be getting support to take their standard treatment. And they said that, because standard treatment needs to be taken multiple times per day, moving to a once-daily injection would be expected to decrease the need for nurse visits. The committee concluded that additional administration costs did not need to be included in the model.

Severity

3.19 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to quality-adjusted life

years (QALYs; a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The estimates did not meet the criteria for applying a severity weight.

Cost-effectiveness estimates

Acceptable ICER

3.20 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted that hypoparathyroidism is a rare condition, and it recognised that there may be challenges with evidence generation. But the committee noted the high level of uncertainty, specifically that:

- There are likely to be differences between the PaTHway trial population and the population who would have palopegteriparatide in the NHS (see section 3.5).
- Standard treatment in PaTHway was suboptimal and would likely not be as effective as standard treatment in the NHS (see section 3.6).
- The primary outcome of PaTHway did not allow for a fair comparison between palopegteriparatide and standard treatment (see section 3.7).
- Functional unblinding in PaTHway may have affected the patient-reported outcomes (see section 3.8).
- The model structure was based on a conceptually weak foundation that was biased against standard treatment (see section 3.9).

- Most of the modelled benefits on mortality, complications and lower resource use were derived from the CPRD analysis which had major limitations (see sections 3.10 to 3.12 and section 3.15).
- The appropriate cost of treating hypocalcaemia and hypercalcaemia adverse events was not clear (see section 3.16).

The committee concluded that it could not set an acceptable ICER threshold until it had seen further analyses to reduce some of this uncertainty.

Cost-effectiveness estimates

3.21 Prior to seeing a revised model, the committee stated a preference on the following assumptions:

- It was appropriate to restrict use of palopegteriparatide to the NAC on standard treatment population as defined in the Second International Workshop 2022 guidelines (see section 3.2).
- The MMRM approach should be used to analyse utility values from PaTHway (see section 3.14).
- The model should assume 100% RDI, and drug wastage because of changing pens, as per the EAG's approach (see section 3.17).
- The model does not need to include administration costs associated with palopegteriparatide (see section 3.18).

But the committee concluded that because of the uncertainties set out in the previous section, all cost-effectiveness estimates presented by the company and the EAG were very uncertain.

Further analyses requested

3.22 The committee considered that the following analyses and information were essential to support its decision making:

- Adjusting the clinical and cost effectiveness of the standard-treatment arm in PaTHway to reflect standard treatment in the NHS, informed by:
  - alternative evidence sources for the effectiveness of standard treatment in the NHS, if available, or
  - clinical expert opinion (see section 3.6).
- A scenario in which the 'independence from therapeutic doses of calcium' component was excluded from the primary outcome of PaTHway and from the health-state definition that would be used in the response-based model (see section 3.7).
- A response-based model with AC and NAC health states defined based on the primary outcome of PaTHway (see section 3.9).
- Using more data from PaTHway and literature sources, and robust, transparent clinical expert opinion to inform the model inputs. The company should ensure that definitions of AC or NAC used to generate these inputs reflected the updated definitions used to define the model health states. That is, they should be based on clinically relevant outcomes such as control of the condition (see section 3.10).
- Providing evidence that the risk of adverse events would be higher in clinical practice than in PaTHway (see section 3.13).
- Basing utility values in the updated model on the revised health states for AC and NAC defined by response to treatment rather than treatment used (see section 3.14).
- A scenario in which resource-use costs are based on resource use in PaTHway (see section 3.15).
- An EAG critique of the company's hypocalcaemia adverse-event cost estimated from the CPRD (see section 3.16).

The committee considered that the following analyses and additional information were not essential for its decision making, but could help to reduce some of the uncertainty:

- Using alternative evidence sources for the effectiveness of standard treatment to inform an indirect treatment comparison with palopegteriparatide (see section 3.6).
- To reduce uncertainty in the estimates of mortality risk:
  - doing scenario analyses with updated estimates of mortality risk using values from the literature
  - exploring the evidence for surrogate relationships between the trial outcomes and mortality
  - provide updated estimates of mortality risk from the CPRD analysis, ensuring that definitions of AC or NAC used to generate these inputs reflect the updated definitions used to define the model health states (see section 3.11).
- To reduce uncertainty in the estimates of complication risk:
  - doing scenario analyses with updated estimates of complication risk using values from the literature
  - exploring the evidence for surrogate relationships between the trial outcomes and complications
  - provide updated estimates of complication risk from the CPRD analysis, ensuring that definitions of AC or NAC used to generate these inputs reflect the updated definitions used to define the model health states (see section 3.12).
- Providing the most recently published value of the 'Hospitalisation for Heart Failure' reference cost (see section 3.16).
- Considering how the resource use for hypocalcaemia and hypercalcaemia might differ from the resource use associated with 'Hospitalisation for Heart Failure' and 'Fluid and Electrolyte Disorders' (see section 3.16).
- Seeking further clinical opinion on the typical length of stay needed to treat hypocalcaemia and hypercalcaemia, the typical cost of such treatment episodes, and variation in length of stay and cost (see section 3.16).

Other factors

Equality

3.23 The committee considered that women, trans men and non-binary people registered female at birth may be at higher risk of post-surgical chronic hypoparathyroidism. They said that this is because of their greater risk of thyroid disease. The committee also heard from consultees that pregnancy may preclude people from having palopegteriparatide, and that people with learning disabilities may have impaired access to treatment. Sex, pregnancy and disability are protected characteristics under the Equality Act 2010. But because its recommendation does not restrict access to treatment for some people over others, the committee agreed these were not potential equality issues.

Uncaptured benefits

3.24 The committee considered whether there were any uncaptured benefits of palopegteriparatide. It heard from the clinical experts that using palopegteriparatide could reduce the need for nurse visits to help with treatment administration. This is because some people need multiple daily visits to help with taking standard treatment. As a once-daily treatment, palopegteriparatide may reduce this. So, the committee concluded that there may be some benefits of palopegteriparatide that may not be captured in the modelling. The committee agreed to take this into account in its decision making.

Conclusion

Recommendation

3.25 The committee concluded that palopegteriparatide should not be used for treating chronic hypoparathyroidism in adults. It noted the high degree of uncertainty in the clinical evidence and economic modelling, and the lack of evidence to justify the modelled benefits. The committee noted that further analyses of the evidence and a different modelling approach may

help to reduce some of these uncertainties. It requested further evidence from the company to support its decision making.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A. Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

James Fotheringham

Vice chair, technology appraisal committee A

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director or principal technical adviser.

Tom Palmer

Technical lead

Zoe Charles

Technical adviser

Jen Upton

Project manager

Lizzie Walker

Principal technical adviser

ISBN: [to be added at publication]