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Draft guidance consultation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: July 2026

Note that this document is not NICE's final guidance on palopegteriparatide. 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using palopegteriparatide in the NHS in England.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 technology appraisal and highly specialised technologies guidance manual.

The key dates for this evaluation are:

Closing date for comments: 12 August 2026

Second evaluation committee meeting: 13 October 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

These are NICE's draft recommendations. If these recommendations become final, palopegteriparatide would not be 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 active vitamin D supplements. Some people also have thiazide diuretics.

For this evaluation, the company asked for palopegteriparatide to be considered only for people with chronic hypoparathyroidism that is not adequately controlled with usual treatment. This does not include everyone who it is licensed for.

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.

The cost-effectiveness estimates are substantially above the range that NICE considers an acceptable use of NHS resources. They are also highly uncertain because the evidence used in the economic model is uncertain.

Because palopegteriparatide is not cost effective in this population, the company has now asked for it to be considered only for people:

- with chronic hypoparathyroidism that is not adequately controlled with usual treatment, and
- who have had at least 2 hospital admissions in the last year.

The company suggests that palopegteriparatide is more likely to be cost effective for this group. 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.

Sustainability

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. In November 2025 the European Society of Endocrinology (ESE) published its guideline on treating chronic hypoparathyroidism in adults. It advises considering PTH replacement treatment for people who have 1 of the following despite optimised standard treatment:

- frequent fluctuations in calcium levels or symptomatic hypocalcaemia
- impaired quality of life attributable to chronic hypoparathyroidism
- reduced kidney function (estimated glomerular filtration rate [eGFR] under 60 ml/min per 1.73m²)
- hypercalciuria (high levels of calcium in the urine) or nephrolithiasis (kidney stones)
- hyperphosphataemia (high levels of phosphate in the blood).

The company asked the committee to evaluate palopegteriparatide for

a subpopulation of people with chronic hypoparathyroidism that is not adequately controlled (NAC) on standard treatment. This is a smaller population than the licensed population (see section 2.1). The company estimated that chronic hypoparathyroidism would be defined as NAC in 10% to 20% of people with the condition in the NHS. It said that the 2025 ESE guideline is expected to become the standard reference for determining suitability for palopegteriparatide and that the criteria for defining NAC were broadly aligned with those in the company's original submission to NICE. The patient and professional groups and the EAG agreed that the ESE guideline could be used to inform eligibility for palopegteriparatide. The committee concluded that it was helpful to have the up-to-date ESE guideline and appropriate to align with it to inform eligibility for palopegteriparatide.

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 clinical expert at the second committee meeting said there was a “huge” unmet need in people with NAC chronic hypoparathyroidism. They explained that the condition being NAC leads to extremely poor quality of life, high symptom burden and high risk of complications in a small subset of people. The clinical expert also said that people report feeling “dramatically” better on PTH replacement treatment because it restores normal physiology. The committee concluded that NAC chronic hypoparathyroidism can lead to very poor quality of life and that there is a high unmet need for a PTH replacement therapy like palopegteriparatide.

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 at 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 said it thought 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 therapeutic active 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 active vitamin D dose was needed to assess whether people could become independent from standard treatment. The EAG also explained that, while the therapeutic 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 included as an option to treat hypercalciuria in the 2025 ESE guideline. The clinical experts agreed that thiazide diuretics have an important role in treating hypercalciuria but noted that they are only used by a small proportion of people and are associated with several side effects. The EAG summarised that standard treatment was suboptimal in PaTHway because the doses of therapeutic calcium and active vitamin D were

reduced and thiazide diuretics were prohibited. The European Medicines Agency was also concerned, describing the standard care in the trial as potentially suboptimal in its European public assessment report (EPAR). The EAG noted that this may have biased the assessment of comparative effectiveness. The committee shared the EAG's concerns. It asked the company to provide more information on standard treatment in the NHS from alternative evidence sources and from clinical expert opinion. It also asked the company to adjust the standard-treatment arm in PaTHway to reflect standard treatment in the NHS including the expected benefit of thiazide diuretics.

After consultation on the draft guidance, the company provided evidence from a Delphi panel exercise of 9 clinical experts. A Delphi panel is a form of structured expert elicitation that aims to reach expert consensus. According to the company, the clinical experts on the panel agreed that standard treatment in PaTHway was representative of standard treatment in the NHS. They also agreed that trial restrictions on active vitamin D and thiazide diuretics would have had little clinically meaningful impact on outcomes and that thiazide diuretics were not widely used. The company said that it did not adjust the standard-treatment arm in its updated model based on this expert elicitation, and because there was no evidence to inform an adjustment. The EAG said that it had the same fundamental concerns about the standard treatment used in PaTHway as it had at the first meeting. It noted that serum calcium levels worsened in the standard-treatment arm during the trial, falling by 0.39 mg/dl by week 26. It pointed out that the company said that even mild changes in serum calcium can impair neuromuscular and neurological function. The clinical expert said that the drop in serum calcium levels observed on standard treatment in the trial was small and transient, because the study adjusted doses of therapeutic calcium to keep calcium within the normal range. They said that there are instances in which this type of dose adjustment happens in clinical practice to reduce the risk of hypercalciuria. The clinical expert also explained that down-titration of therapeutic calcium and active

vitamin D was needed in PaTHway to guard against trial-induced hypercalcaemia (high levels of calcium in the blood), which is a risk with palopegteriparatide. So, the reduction in standard-treatment doses was necessary as a function of the randomised controlled trial design.

The committee noted the results from the Delphi panel and the clinical expert feedback. It accepted that thiazide diuretics were not widely used in NHS practice. It noted that the company had not adjusted the standard-treatment arm in PaTHway to reflect standard treatment in the NHS. It appreciated that the trial design of PaTHway meant that reductions in therapeutic calcium and active vitamin D in the standard-treatment arm were needed to maintain blinding in the study. But this did not mean that standard treatment in the trial was optimal. The committee still believed that the trial design meant that standard treatment in the trial may not be as effective as standard treatment in the NHS. It concluded that this contributed to the substantial uncertainty around the effectiveness of palopegteriparatide compared with standard treatment in the NHS (see section 3.7).

Primary outcome

3.7 The primary outcome of PaTHway was a composite outcome at week 26 in which all 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 during 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 during 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 treatment, but that it did not show that palopegteriparatide was more clinically effective than standard treatment. The company explained that the multicomponent 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 said that the primary outcome provided no direct evidence of clinical benefit. The company said that quality-of-life outcomes were measured in PaTHway and did show a benefit for palopegteriparatide.

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 acknowledged that the results for the primary outcome suggested that palopegteriparatide was an effective PTH replacement treatment. But it considered 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. It 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.

After consultation on the draft guidance, the company provided figures showing that excluding independence from therapeutic calcium from the primary outcome did not change the number of responders in either arm of the trial. Excluding independence from both calcium and active vitamin D increased the number of responders in the placebo (standard-treatment) arm. These figures are considered confidential by the company so cannot be reported. The EAG maintained that the only relevant outcome for the standard-treatment arm was serum calcium in the normal range. The committee thought that the company's new analysis addressed some of the concerns about the primary outcome. But it concluded that the design of the primary endpoint, combined with the mandated reductions in standard treatment (see section 3.6), meant there was still uncertainty in the comparative effectiveness of palopegteriparatide and standard treatment.

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 having palopegteriparatide reported better health-related quality of life than people having 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 therapeutic calcium dose by week 6 and had largely discontinued active vitamin D by week 4. In contrast, people in the standard-treatment arm remained on high therapeutic calcium doses throughout the 26-week period. Active 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's original economic model was a 3-state on-or-off-treatment model (adequately controlled [AC], NAC, and death). People entered the model in the AC health state if they were starting palopegteriparatide or in

the NAC health state if they were having 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. That is, there was no possibility of response when having standard treatment. 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 noted the assumption that everyone having palopegteriparatide was in the AC health state and everyone having standard treatment in the NAC health state. It highlighted that this 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 EAG suggested that a viable alternative would be a response-based model with treatment response based on the primary outcome of PaTHway. The committee agreed that the model structure was flawed and asked the company to provide a response-based model.

After consultation on the draft guidance, the company provided a response-based model using the primary endpoint from PaTHway (see section 3.7) to inform health states and utilities. The company maintained its assumption that it was not possible to have a response with standard treatment. So, 1 person having standard treatment (that is, 4.8% of the standard-care arm) who met the primary endpoint was not included in the response health state. The company argued that response was not biologically plausible on standard treatment and that this was supported

by its Delphi panel of clinical experts. The company suggested that the person who met the primary endpoint on standard treatment was likely to have recovered residual parathyroid gland function, rather than having a response to standard treatment. To account for this, the company's model assumed a similar proportion in both arms had restored gland function and removed the equivalent percentage (4.8%) from both treatment arms. The company said that, in NHS clinical practice, people's residual parathyroid function would be tested, and their standard treatment adjusted accordingly, before they could be considered eligible for palopegteriparatide. The clinical expert said that it was possible for someone with hypoparathyroidism to spontaneously recover PTH function and that this was usually in the first 6 months after diagnosis. But they said that the rate of recovery is extremely low. Based on the published literature, the clinical expert estimated that this would be 1% or less overall. The EAG said it was concerned that the company had adjusted trial response rates without strong supporting evidence. It said that if trial outcomes were adjusted, it should keep the relative treatment effect seen in the trial and not simply subtract the same percentage from both arms. It thought that the clinical evidence from the trial should not be superseded by clinical expert opinion from the Delphi panel. The EAG preferred to align with the clinical evidence from the trial and assumed that it was possible to have a response on standard treatment. It said that the model structure was flawed in that people entered it as 'responders' or 'non-responders', implying that the treatment benefit was instant. In real life, response would be assessed after 6 months, although it noted this was unlikely to have a large impact on results. The EAG said it remained concerned that PaTHway's design and composite endpoint (see section 3.7) did not allow a fair comparison of the interventions, even using response-based data in the model.

The committee agreed that the company's response-based economic model was more appropriate than its original treatment-based model. It acknowledged the EAG's concerns around the trial's design and

composite endpoint. It understood the company's rationale for excluding 1 person in the standard-treatment arm who met the primary endpoint. The committee understood that spontaneous recovery of parathyroid function is possible but that it occurs at a low rate and usually in the first 6 months after diagnosis. It discussed how the 4.8% recovery rate observed in the standard-treatment arm of the trial was likely to be an overestimate of the true proportion. It said that this is because it represented 1 patient in the trial, which included only a small number of participants. It would have preferred to see a more robust and accurate estimate from a larger number of patients but acknowledged that this was not possible because of the limited evidence base. The committee concluded that the rate of recovery was likely to be low, around 1%, as reflected in the literature. Because of this, the committee considered analyses assuming a 1% rate of spontaneous recovery in both arms. But the committee emphasised that this assumption was still associated with considerable uncertainty and limitations in the available evidence, and that it was not optimal to discard trial evidence in favour of expert opinion. It noted that this assumption was based on the best available data and expert opinion, but that it would have preferred more robust, prospective data to inform it. The committee concluded that the approach taken in this case was not optimal, and that future evaluations should use more clearly validated and transparently derived trial-based estimates wherever possible.

Definitions of AC and NAC in the CPRD for informing 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. At the first committee meeting, the company used the following definitions to differentiate between AC and NAC chronic hypoparathyroidism:

- NAC: more than 5 outpatient visits and 1 or more inpatient visit per patient per year
- AC: 5 or fewer outpatient visits and less than 1 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 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 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. This is often because people with poorly controlled hypoparathyroidism may avoid seeking emergency care because of poor experiences in the

emergency department (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.

After consultation on the draft guidance, the company changed its definition of AC and NAC chronic hypoparathyroidism in the CPRD analysis to:

- NAC: 1 or more inpatient visits per year, with hypoparathyroidism as the primary or secondary diagnosis
- AC: all remaining patients without complications.

The company said that its Delphi panel experts agreed that hypoparathyroidism-related healthcare use was a clinically valid way to identify people whose condition was NAC. They also agreed that there was a clear difference in healthcare-resource use between AC and NAC chronic hypoparathyroidism. The EAG reiterated its concerns around defining AC and NAC by healthcare use, not clinical severity. It said that the revised NAC definition was very narrow, and based on a small sample, which is likely to capture only people with the most

severe hypoparathyroidism with the highest resource use. The EAG was concerned that the high inpatient costs in this group may be driven by a small number of people, which was suggested by the large variation in inpatient costs. It pointed out that the costs had been much lower using the original NAC definition, and concluded that overall the NAC costs were highly uncertain and probably overstated, inflating modelled cost savings. The committee questioned why the company had not compared resource use in PaTHway with CPRD, noting that it would have been helpful to see the relative increase in hospital admissions for people who met the trial primary endpoint compared with people who did not. But the company said that the numbers of clinical events were too low in both arms for this to be useful. This was because of more intense monitoring in the trial compared with real-world practice, which the company said would have prevented many events that would have led to healthcare-resource use. The committee noted feedback from the draft guidance consultation and from the clinical expert at the second committee meeting that there was inconsistent coding in clinical practice because of the rarity of hypoparathyroidism and lack of clinical awareness. This meant that the CPRD did not reliably identify related admissions or outpatient and emergency attendances. It recalled that the patient experts had said that people with poorly controlled hypoparathyroidism would not necessarily have any inpatient admissions over the course of a year. So, they may not meet the company's updated NAC criteria. The committee considered that these factors limited the robustness of the data from the CPRD. The committee also remained concerned that the following multiple different definitions of AC and NAC were still used in the trial and in the model, and that this substantially increases the uncertainty in the model:

- NAC criteria from the 2025 ESE guideline for informing eligibility for palopegteriparatide

- the trial primary outcome for AC (responder) or NAC (non-responder) health states in model
- AC and NAC using resource-used based criteria from the CPRD analyses for model inputs.

The committee agreed that defining AC and NAC by resource use led to substantial uncertainty in the resulting cost-effectiveness analyses and noted that these assumptions had a substantial impact on the cost-effectiveness results. The committee thought the company's updated NAC definition could be too narrow. It thought that limiting it to only people with a hypoparathyroidism-related inpatient admission likely meant that only people with a very severe subtype were included. So, it thought that it was unlikely that it would align with the ESE's definition of NAC chronic hypoparathyroidism that would inform eligibility for palopegteriparatide. The committee concluded that it preferred to define AC and NAC based on the company's original definition from the first committee meeting. It considered that this definition still had substantial limitations. But it was more likely to align with the definition of NAC in the ESE guideline because it is based on a larger population for NAC than the updated definition. It also took into account that many hypoparathyroidism-related admissions were likely not to have been coded correctly, which could overestimate health-state costs. The committee also noted that the NAC health-state costs generated using the original definition were lower than those generated using the updated definition (see section 3.15). The committee noted the substantial uncertainty associated with this assumption and that it had a substantial impact on the cost-effectiveness results. So, it preferred to use the more conservative estimate, based on the original definition.

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 this in the original model so that palopegteriparatide reduced mortality compared with standard treatment. Although the EAG accepted that palopegteriparatide may 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 compared with 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. It asked the company to provide evidence for a mortality benefit with palopegteriparatide.

After consultation on the draft guidance, the company said it was unable to identify any appropriate alternative data sources for mortality. So, it updated its model so that there was no difference in mortality between the NAC and AC groups. It applied the same risk of death to both (2.89 times higher than the general population, sourced from published literature). So, the model did not assume that palopegteriparatide improves survival compared with standard treatment. This was in line with the EAG's preferred assumption. The committee concluded that the company's updated mortality assumptions were appropriate.

Modelling of complications

3.12 Complications in the model were captured by a linked event-based sub-model. The short timeframe of the trial meant that any effect of palopegteriparatide on long-term complications did not have time to emerge. 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. It asked the company to provide evidence for the impact of palopegteriparatide on complications.

After consultation on the draft guidance, the company said it could not find any other evidence to update complication risks. It also said that the CPRD data could not be aligned with the response-based states, so the original complication rates were retained. The EAG said that the underlying issue remained and that the company analysis relied on the strong assumption that resource use was a proxy for complication rates. The committee acknowledged clinical expert opinion that emerging longer-term trial evidence may indicate an impact of palopegteriparatide on longer-term complications, including improved renal and skeletal outcomes. But the committee thought that the effect of palopegteriparatide on the incidence of complications was still uncertain with no other evidence other than a proxy relationship between resource use and

complication rates to support it. The committee thought that the costs associated with complications would be captured in the all-cause costs from its preferred analysis of CPRD data to inform health-state resource use (see section 3.16). So, it agreed that it was not appropriate to assume additional costs associated with complications. The committee acknowledged that any potential quality-of-life benefit of palopegteriparatide in reducing complications was uncertain. So, it asked the company to provide analyses with and without an effect of palopegteriparatide on complication rates.

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 modelled rates of adverse events. 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 believed 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. The committee asked the company to provide evidence that the risk of adverse events would be higher in clinical practice than in PaTHway.

After consultation on the draft guidance, the company presented the results of its Delphi panel exercise, in which clinical experts agreed that the number of serious symptomatic hypocalcaemia events in PaTHway

could have been artificially low. The clinical experts on the panel also agreed that, typically, someone whose hypoparathyroidism was NAC in practice had at least 2 to 3 symptomatic hypocalcaemia events a year, with 2 to 3 needing an inpatient hospital admission. So, the company kept the assumption that any grade of adverse event from the trial should be used to calculate the modelled rates of adverse events. The EAG said that clinical opinion was not robust enough to justify this assumption, which meant that even grade 1 and 2 adverse events were assumed to result in needing admission to hospital. It also said that the CPRD data suggested that the number of inpatient admissions for symptomatic hypocalcaemia was much lower than the Delphi panel estimate. The clinical expert said that, because hypoparathyroidism was a rare disease, it was possible that hypocalcaemia events were not coded correctly, hence the low numbers in the CPRD data. They also pointed out that intensified monitoring and improved access to healthcare in trials means that adverse-event rates in trials do not always apply to real-world practice. The committee acknowledged that the rates in the trial and CPRD data may not reflect what is seen in the NHS. But it concluded that it was not reasonable to assume that grade 1 and 2 adverse events had the same consequences as grade 3 and 4 adverse events. The committee also noted uncertainty about the appropriate costs for adverse events and whether these costs would be double counted with health-state resource-use costs. It preferred not to include further costs associated with adverse events and complications because these were likely already included in the all-cause costs from the original CPRD analysis (see section 3.16).

Utility values

3.14 The company calculated utility values using EQ-5D data collected in PaTHway. In its original economic model, 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 week 10. 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 and concluded that the MMRM approach should be used. After consultation on the draft guidance, the company updated its model to use MMRM values. The committee concluded that the company's revised utility values were appropriate.

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 thought that the size of cost savings projected by the company's model was not credible. 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 captured resource use unrelated to chronic hypoparathyroidism, such as hospitalisations because of comorbid conditions, and so did not align with the NICE reference case. It thought that the higher healthcare use in NAC patients may relate to these comorbid conditions rather than the severity of hypoparathyroidism itself. This is likely to overstate the cost savings resulting from improved disease control. The EAG said that the significant disparity in health-state costs

between the AC and NAC was a major driver of cost effectiveness. At the first meeting the committee was concerned that the costs generated from the CPRD analysis were not reliable and asked the company to provide more robust model inputs. It also asked for a scenario with resource-use costs based on PaTHway.

After consultation on the draft guidance, the company updated the health-state resource-use costs to reflect the revised definitions of AC and NAC from the updated CPRD analysis (see section 3.10). This meant that only costs for people with a hypoparathyroidism-related admission were included in the NAC health state. It removed costs for hypo- and hypercalcaemia after the EAG flagged concerns that they might be double counted – that is, included in healthcare resource-use costs and also costed separately as adverse events (see section 3.16). The company said its updated analysis was conservative because hypoparathyroidism-specific costing is likely to underestimate the overall burden, because the condition affects multiple organs. It also said that AC costs were likely to be overestimated because the updated definition of NAC excluded some people with high hypoparathyroidism-related healthcare costs. As a result, these higher-cost patients would be included in the AC group, increasing estimated costs for the AC group. The company did not provide a scenario using PaTHway resource-use estimates because it considered these would not be representative of the NHS (see section 3.10). The EAG was concerned that the company's large predicted cost savings were driven by highly uncertain assumptions about healthcare resource-use costs. The EAG also questioned whether the high inpatient costs in the NAC group were influenced by a small number of very expensive cases, given the large variation in inpatient costs and the much lower costs in the company's original NAC group. Overall, the EAG concluded that NAC costs were probably overstated, which would inflate the modelled cost savings for palopegteriparatide (see section 3.10). In its base case, the EAG therefore removed all health-state costs. It acknowledged that this was not plausible. But it explained that good

evidence was needed to justify that the large cost savings with palopegteriparatide would be realised in clinical practice. The EAG said that it believed that cost savings could exist but not ones as large as suggested by the company's analysis.

The committee agreed with the EAG's comments about the company's updated health-state costs. It was concerned that using the company's updated definitions of AC and NAC resulted in similar health-state costs for AC but higher costs for NAC, including substantially higher inpatient costs. It thought this was likely to be because patients with more severe illness in the updated definition resulted in higher costs per person. Despite the concerns with the CPRD analysis, the committee did not think it was plausible to assume no difference in health-state costs between palopegteriparatide and standard treatment, as in the EAG base case. It acknowledged that the rarity of the condition may increase the uncertainty of the CPRD analysis, because of lack of clinical awareness and inconsistent coding of hypoparathyroidism in clinical practice (see section 3.10). It also acknowledged that the rarity of the condition meant that more robust evidence to inform the health-state costs was unlikely to be available. So, the committee accepted that it was reasonable to use the cost estimates from the CPRD, despite the substantial uncertainty in these analyses. But it agreed with the EAG that the estimated costs in the NAC health states were likely overstated in the company's original and updated analyses. The committee recalled its preference for using the original definition of NAC in the CPRD analysis, which was based on a broader NAC population (see section 3.10). It concluded that it preferred the health-state resource-use costs estimated using the company's original definition of AC and NAC. But it also concluded that these costs still likely overestimated resource use for the NAC health state because they included all-cause costs, and this would inflate the modelled cost savings for palopegteriparatide. The committee agreed that it would take this uncertainty into account in its decision making.

Adverse-event and complication 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'. 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. 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. The company considered the exact value to be confidential and so it cannot be reported here. The committee was uncertain about what the appropriate cost would be for these adverse events and asked the company to provide additional evidence. It thought that, in the absence of a specific NHS reference cost, using a cost derived from the CPRD could be useful.

After consultation on the draft guidance, the company updated its base case to include the mean cost of an admission for symptomatic hypocalcaemia from the CPRD. The EAG agreed that it was appropriate to use CPRD values but questioned how the calculation had been done. The model requires a cost per event so if patient-level averages were used it would not match and could bias results if people with frequent

admissions had different costs. It also noted that the figure was calculated from a small number of patients and that the standard deviation was larger than the mean value, indicating that the estimate was highly uncertain. It said that this was important because the model predicts large cost savings, which depend on this estimate. The EAG provided an alternative scenario using mean cost per event. The clinical expert said that symptomatic hypocalcaemia drives most visits to hospital. But the committee noted that removing these events from the health-state costs made little difference to overall health-state costs in the updated CPRD analysis. The committee thought this lacked face validity. The committee recalled its preference for using all-cause costs from the original CPRD analysis to estimate resource use for the NAC and AC health states (see section 3.10). It also recalled that the clinical expert said that because hypoparathyroidism was a rare disease it was possible that hypocalcaemia events were not coded correctly. It noted the EAG's concerns in its critique of the company's updated CPRD analysis that inpatient costs for adverse events might have been double counted in this analysis (see section 3.13). It also thought there could be double counting of the costs of complications if these were included separately. It concluded that it preferred not to include further costs associated with adverse events and complications because these were likely already included in the all-cause costs from the original CPRD analysis.

Drug wastage

3.17 The company did not include drug wastage in its original 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%. After consultation, the company included drug wastage and set the RDI to 100% to align with the EAG's preferred assumptions. The committee concluded that these assumptions were 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 having 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 (a severity modifier) to quality-adjusted life years (QALYs) 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 technology appraisal and highly specialised technologies guidance notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £25,000 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 (see section 3.24). The committee noted that hypoparathyroidism is a rare condition, and it recognised that there may be challenges with evidence generation. It also acknowledged the challenges with using real-world evidence from the CPRD because of the lack of clinical awareness of hypoparathyroidism and inconsistent coding in clinical practice. It recalled that section 6.2.33 of the NICE technology appraisal and highly specialised technologies guidance manual states that if evidence generation is particularly difficult because of the rarity of the condition, the committee may be able to make recommendations accepting a higher degree of uncertainty. The committee concluded that it could accept a higher degree of uncertainty in its decision making for this evaluation. It recalled that there were several areas of substantial uncertainty, including:

- 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).
- The effectiveness of palopegteriparatide compared with standard treatment was uncertain because:
  - standard treatment in PaTHway was suboptimal (see section 3.6)
  - there were concerns about the design of the primary outcome (see section 3.7)

  - functional unblinding may have affected the patient-reported outcomes (see section 3.8).
- Different definitions of AC and NAC were used in the trial and model:
  - NAC criteria from the 2025 ESE guideline for informing eligibility for palopegteriparatide
  - the trial primary outcome for the AC (responder) and NAC (non-responder) health states in the model
  - AC and NAC using resource-used based criteria from the CPRD analyses for model inputs.
- In the model, lower resource-use estimates for palopegteriparatide compared with standard care were derived from the CPRD analysis, which had major limitations. This likely inflated the modelled cost savings for palopegteriparatide and was a key driver of cost effectiveness (see section 3.10 and section 3.15).

Taking into account the challenges with evidence generation, the uncaptured benefits and substantial uncertainty, the committee concluded that an acceptable ICER would be around £25,000 per QALY gained.

Committee's preferred model assumptions and ICER

3.21 The committee's preferred model assumptions were:

- a response-based structure, considering analyses with a 1% rate of spontaneous recovery in both arms (see section 3.9)
- CPRD definitions of AC and NAC from the original committee meeting used to inform all-cause health-state costs (see section 3.10 and section 3.15)
- a hazard ratio of 2.89 for mortality for both model arms (see section 3.11)
- no effect of palopegteriparatide on complication rates (see section 3.12)
- utility values based on MMRM analysis (see section 3.14)

- no further costs associated with adverse events and complications (see section 3.16)
- drug wastage and 100% RDI (see section 3.17)
- no additional administration costs (see section 3.18).

Based on these assumptions, the committee's preferred probabilistic ICER was £144,296 per QALY gained. The committee concluded that this was substantially above the acceptable ICER agreed for this evaluation of around £25,000 per QALY gained (see section 3.20).

Proposed subgroup with 2 previous hospital admissions

3.22 After the second committee meeting, the company acknowledged that palopegteriparatide may not be a cost-effective option in the full population of people with NAC chronic hypoparathyroidism. So, the company proposed that NICE evaluate it for a subgroup of people who had been admitted to hospital at least twice in the previous year. The committee recalled the high unmet need for a PTH replacement treatment for people with chronic hypoparathyroidism. It noted the clinical expert's comments at the second committee meeting that evidence on effective treatments is limited because hypoparathyroidism is rare. It also noted the clinical expert's comments that professional groups were keen to work with NICE so that the people most likely to benefit can access palopegteriparatide. But the committee considered that there was substantial uncertainty about whether this subgroup would be implementable in NHS practice. It recalled how the patient experts had explained that people with poorly controlled hypoparathyroidism may try to manage their condition in primary care because of poor experiences with emergency care, so may not have any inpatient admissions over the course of a year (see section 3.10). The committee also noted that this subgroup had not been pre-specified in the PaTHway trial. So, the committee requested the following additional analyses and information from the company:

- The definition of the proposed subgroup for the updated decision problem, including:
  - whether the definition of admission to hospital can be linked to a clinical event, such as symptomatic hypocalcaemia, so avoiding the need to use resource use as a proxy
  - whether hospital admissions would include inpatient stays only
  - whether hospital admissions would be for any reason, or directly attributable to hypoparathyroidism only and, if so, how clearly this is defined in clinical practice
  - clinical and patient expert opinion on whether and how the proposed subgroup would be implementable in NHS practice.
- The generalisability of the PaTHway trial to the proposed subgroup, including:
  - how well the trial data reflects the updated subgroup
  - analysis using efficacy data based only on people meeting the new subgroup criteria
  - data on the number and type (inpatient, day case, other) of admissions to hospital for patients in the trial, before and after starting trial treatment.
- CPRD analysis for the proposed subgroup, including:
  - an analysis of CPRD data for the proposed subgroup (2 or more hospital admissions in the previous year) and the corresponding comparator group (fewer than 2 hospital admissions in the previous year) showing (per person):
    - ◊ the number of patients in each group
    - ◊ the clinical characteristics of patients in each group
    - ◊ the total annual health-state costs
    - ◊ the total annual inpatient costs
    - ◊ the inpatient costs as a percentage of the total costs
    - ◊ the total per-cycle costs

- ◊ if possible, all these for people with 2 or more hospital admissions in the previous year (rather than the same year the resource-use data is from)

– aligning the criteria to define the proposed subgroup in the CPRD analysis with the definition of the proposed subgroup for the decision problem (see above).

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 that 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. The committee also heard from patient and professional groups that the condition's psychological and emotional burden were not captured by the EQ-5D, for example depression and cognitive fog. So, the committee concluded that there may be some benefits of palopegteriparatide that may not be captured in the modelling. The committee took these factors into account when agreeing its preferred ICER threshold (see section 3.20).

Conclusion

Recommendation

3.25 The committee noted the substantial uncertainty in the clinical evidence and economic modelling. It recognised that hypoparathyroidism is a rare condition with associated challenges with evidence generation. So, it concluded that it could accept a higher degree of uncertainty in its decision making (see section 3.20). But the committee noted that there was substantial uncertainty with both the clinical evidence base and the inputs to the economic model. So, the committee concluded that an acceptable ICER for this evaluation would be around £25,000 per QALY gained. The committee noted that the ICER incorporating its preferred assumptions was substantially higher than the acceptable ICER (see section 3.21). It concluded that palopegteriparatide had not been shown to be cost effective for the full population of people with NAC chronic hypoparathyroidism. So, it should not be used.

After the second committee meeting, the company asked for palopegteriparatide to be considered only for people who have had at least 2 hospital admissions in the last year. The committee will consider the cost effectiveness of palopegteriparatide in this subgroup when the company submits further analyses.

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.

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