

palopegteriparatide solution for injection in pre-filled pen (Yorvipath®)

Ascendis Pharma UK Limited

04 September 2026

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process
palopegteriparatide (Yorvipath®) is not recommended for use within NHSScotland.

Indication under review: the treatment of adults with chronic hypoparathyroidism.

Evidence from a double-blind, phase III study demonstrated that at 26 weeks, a significantly higher proportion of patients in the palopegteriparatide group achieved the primary composite outcome (evaluating calcium control, independence from conventional therapy and dosing of study medicines) compared with placebo.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

The submitting company has indicated their intention to make a resubmission.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Palopegteriparatide is a pro-drug linked to an inert methoxypolyethylene glycol (mPEG) carrier which is changed in the body into teriparatide, a shortened form of parathyroid hormone. Teriparatide replaces the missing hormone in patients with hypoparathyroidism, acting through bone tissue and the kidneys to help restore calcium levels.^{1, 2}

The recommended starting dose of palopegteriparatide is 18 micrograms once daily administered by subcutaneous injection; dose range is from 6 to 60 micrograms per day. For more information on adjusting doses of palopegteriparatide, vitamin D, or calcium supplementation, please see the Summary of Product Characteristics (SPC).¹

1.2. Disease background

Hypoparathyroidism is a rare endocrine disorder that is characterised by absent or deficient production of parathyroid hormone. Approximately 75% of cases occur following neck surgery, however less common aetiologies include autoimmune or genetic conditions with some cases being idiopathic. Chronic hypoparathyroidism is characterised by persistent hypocalcaemia and inappropriately low or normal parathyroid hormone levels lasting for more than 6 to 12 months. Under normal conditions, parathyroid hormone and its downstream hormone calcitriol act on bone, the kidneys and intestine to regulate calcium and phosphate levels. In hypoparathyroidism, reduced parathyroid hormone activity causes hypocalcaemia due to decreased calcium reabsorption from the urine, insufficient calcitriol production to absorb calcium from the intestines and a reduction in resorption of calcium from the bone. In addition, a reduction in renal reabsorption of calcium and excretion of phosphate causes hypercalciuria and hyperphosphatemia. There are a broad range of symptoms and complications which affect multiple organs, vary in severity and can have a substantial impact on quality of life. These can include neuromuscular and psychiatric symptoms, increased bone density and risk of infections, cataracts, cardiovascular disease and chronic kidney disease. Some symptoms such as seizures and cardiac arrhythmias can be life threatening.³⁻⁶

1.3. Company proposed position

The submitting company has requested that palopegteriparatide is restricted for use in adults with chronic hypoparathyroidism who are not adequately controlled using conventional therapy.

1.4. Treatment pathway and relevant comparators

The aim of treatment for chronic hypoparathyroidism is to relieve symptoms of hypocalcaemia, improve quality of life and long-term prognosis. Conventional therapy includes adequate dietary calcium intake with or without oral calcium supplementation, and oral activated vitamin D analogues (for example, calcitriol or alfacalcidol). Symptomatic severe hypocalcaemia may require acute intravenous calcium replacement. Hyperphosphatemia and hypomagnesaemia should also be corrected to within normal range if necessary. There are limitations with conventional therapy which can include fluctuations in calcium levels, a high pill burden, hyperphosphatemia, hypercalciuria and renal complications. Some patients may require treatment with a thiazide diuretic to normalise hypercalciuria. Guidelines recommend parathyroid hormone replacement

therapy in patients with chronic disease who despite optimisation of calcium and activated vitamin D treatment, experience at least one of the following: frequent fluctuations in calcium levels or symptomatic hypocalcaemia, impaired quality of life, reduced renal function, hypercalciuria or hyperphosphatemia.⁴ There are currently no parathyroid hormone replacement therapies licensed for chronic hypoparathyroidism and available in Scottish practice. Clinical experts consulted by SMC confirmed that optimised activated vitamin D therapy and calcium supplementation is the predominant treatment for chronic hypoparathyroidism and there are limited additional options for those not adequately controlled on this conventional therapy. The submitting company considered that conventional therapy with oral active vitamin D analogues with or without calcium supplements was the most relevant comparator for this submission.

1.5. Category for decision-making process

Eligibility for a PACE meeting

Palopegteriparatide meets SMC orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support palopegteriparatide for the indication and proposed positioning is from the PaTHway study as detailed in Table 2.1.

Table 2.1. Overview of relevant studies^{2, 6}

Criteria	PaTHway study
Study design	Randomised, double-blind, placebo-controlled, phase III study with open-label extension period
Eligible patients	- Adult patients with chronic hypoparathyroidism of postsurgical, auto-immune, genetic, or idiopathic aetiology for at least 26 weeks. - Treatment with calcitriol ≥ 0.5 micrograms/day, or alfacalcidol ≥ 1.0 micrograms/day plus elemental calcium ≥ 800 mg/day for at least 12 weeks prior to screening with stable doses for at least 5 weeks prior to screening. Occasional (≤ 2 per week) as required doses of calcium and/or active vitamin D was permitted for symptomatic hypocalcaemia. - Optimisation of supplements prior to randomisation to achieve target serum levels of: - Albumin-adjusted serum calcium 7.8 to 10.6 mg/dL (or 1.95 to 2.64 mmol/L) or ionised serum calcium 4.40 to 5.29 mg/dL (or 1.10 to 1.32 mmol/L), that is within or slightly below the normal range. 25(OH) vitamin D levels of 20 to 80 nanograms/mL (49 to 200 nmol/L). - Magnesium level ≥ 1.3 mg/dL (0.53 mmol/L). - A 24-hour urinary calcium excretion of ≥ 125 mg/24 hours. - eGFR ≥ 30 mL/min/1.73 m².
Treatments	Palopegteriparatide or matching placebo once daily self-administered by subcutaneous injection in addition to conventional therapy (active vitamin D and elemental calcium). The starting dose was 18 micrograms with individual progressive titration to an optimal dose in 3 microgram per day increments in ≥ 7 -day intervals according to the treatment algorithm based on serum calcium levels (dosing range 6 to 60 micrograms per day). At

	the start of the study active vitamin D doses were reduced by 33 to 50% at treatment initiation in all patients. Where serum calcium levels were low within seven days of starting study treatment or changed dose of study treatment, routine calcium supplement dose and/or vitamin D dose could be increased. Concomitant use of thiazide diuretics was not permitted. On completion of the double-blind period patients could enter the open-label extension periods and receive palopegteriparatide.
Randomisation	Patients were randomised 3:1 and stratified according to aetiology of hypoparathyroidism (post-surgical versus other)
Primary outcome	The proportion of participants with all of the following at week 26: • Albumin-adjusted serum calcium within the normal range (8.3 to 10.6 mg/dL) measured within 4 weeks prior to and on week 26. • Independence from active vitamin D. • Independence from therapeutic doses of elemental calcium. • No increase in prescribed trial medicine within 4 weeks prior to week 26 visit. Independence from active vitamin D was defined as a daily dose equal to zero on all days and use of any PRN active vitamin D on no more than 7 days during the 4 weeks before the week 26 visit. Independence from therapeutic calcium was defined as an average daily standing dose of ≤ 600 mg and use of PRN doses on no more than 7 days during the 4 weeks before the week 26 visit.
Secondary outcomes	Key secondary patient-reported outcomes include the change in score from baseline to week 26 in: • HPES - Symptom - Physical domain • HPES - Symptom - Cognitive domain • HPES - Impact – Physical Functioning domain • HPES - Impact – Daily Life domain • SF-36 - Physical Functioning subscale Other secondary outcomes measured at week 26 include: • Mean dose of elemental calcium • Mean dose of activated vitamin D • Mean daily pill burden of active vitamin D and calcium • Mean albumin-adjusted serum calcium
Statistical analysis	A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. The primary outcome followed by the key secondary patient-reported outcomes (in the order listed above) were tested sequentially. Efficacy analyses were conducted in the ITT population which included all patients who were randomised and received at least one dose of the blinded study medicine.

Abbreviations: dL = decilitre; eGFR = estimated glomerular filtration rate; ITT = intention to treat; HPES = Hypoparathyroidism Patient Experience Scale; L = litre; mmol = millimoles; nmol = nanomoles; PRN = pro re nata (as needed); SF-36 = 36-Item Short Form Survey

2.2. Evidence to support the positioning proposed by the submitting company

The submitting company considered that the intention to treat (ITT) population of the PaTHway study represented the proposed positioning. The results have been detailed in Table 2.2.

Table 2.2. Primary and select secondary efficacy outcomes at week 26 for the PaTHway study (ITT population).^{2, 6}

	Palopegteriparatide (n=61)	Placebo (n=21)
Composite primary outcome		
Responders, n	48	1
Proportion, (%) (95% CI)	79% (66 to 88%)	4.8% (0.1 to 24%)
p-value	<0.001	
Individual components of primary outcome		
Albumin-adjusted serum calcium in normal range	80%	48%
Independence from active vitamin D ^a	98%	24%
Independence from therapeutic doses of calcium ^b	93%	4.8%
No increase in prescribed study medicine within 4 weeks of week 26	93%	57%
Select secondary outcomes		
Mean dose of elemental calcium at baseline (mg)	1748.03	2104.76
Mean dose of elemental calcium at week 26 (mg)	274.17	1847.39
Mean dose of activated vitamin D at baseline (micrograms)	0.992	0.940
Mean dose of activated vitamin D at 26 weeks (micrograms)	0.000	0.618
Mean daily pill burden at baseline (n)	6.7	6.7
Mean daily pill burden at week 26 (n)	0.5	5.4
Mean albumin-adjusted serum calcium at baseline (mg/dL)	8.80	8.63
Mean albumin-adjusted serum calcium at week 26 (mg/dL)	8.94	8.22

Abbreviations: CI = confidence interval; mg = milligrams; dL = decilitre

^aDaily dose equal to zero and use of as required doses on ≤ 7 days in the 4 weeks prior to week 26. ^bAverage daily dose of ≤ 600 mg and use of as required doses on ≤ 7 days in the 4 weeks before the week 26.

A post hoc analysis was conducted to assess change in renal function at 26 weeks. In the palopegteriparatide group the mean estimated glomerular filtration rate (eGFR) increased by 7.9 mL/min/1.73m² from 67.3 mL/min/1.73m² at baseline. In the placebo group, there was a slight decrease by -1.9 mL/min/1.73m² from 72.7 mL/min/1.73m² at baseline.⁷

Following completion of the 26-week double-blind period of the PaTHway study, 96% (79/82) of patients entered the 156-week open-label extension study. All patients randomised to the placebo group for the double-blind period were started on palopegteriparatide in addition to their current conventional therapy. At week 52 (including 26 weeks of the double-blind phase) no patients were taking active vitamin D and 95% were independent from therapeutic doses of calcium. In patients randomised to placebo during the double-blind phase, albumin-adjusted serum calcium levels increased over approximately 12 weeks and were maintained within normal range to week 52. In patients randomised to palopegteriparatide in the blinded phase, bone resorption biomarker, C-terminal telopeptide of type 1 collagen (CTX) and bone formation biomarker, procollagen type 1 N-terminal propeptide (P1NP) trended toward age- and sex-matched norms at week 52 indicating a restoration of closer to normal bone physiology. Mean bone mineral density Z-scores also trended

toward age- and sex-matched norms. Week 156 was completed by 89% (73/82) of patients, of these 96% were no longer taking conventional therapy and 88% had normal albumin-adjusted serum calcium. The mean increase in eGFR of 8.8 mL/min/1.73m² to 78 mL/min/1.73m² from baseline was similar to the palopegteriparatide group at 26 weeks and mean 24-hour urine calcium levels remained below the upper limit of normal. Additional data provided by the company at week 182 were consistent with results at week 52 and week 156.⁸⁻¹⁰

2.3. Health-related quality of life outcomes

There were statistically significant improvements in all key secondary outcomes in the palopegteriparatide group compared with the placebo group from baseline to week 26. The results have been detailed in Table 2.3.^{2, 6}

Table 2.3: Patient-reported outcomes included in the hierarchical testing procedure in the ITT population.²

	Palopegteriparatide (n=59)	Placebo (n=19)
HPES - symptom scores: LSM change from baseline at week 26		
Physical domain ^a	-21.01	-4.81
Cognitive domain ^a	-20.49	-6.16
HPES – impact scores: LSM change from baseline at week 26		
Physical functioning domain ^a	-18.29	-1.01
Daily life domain ^a	-17.65	-0.36
36-item Short Form Survey score: LSM change from baseline at week 26		
Physical Functioning subscale ^a	5.285	0.122

Abbreviations: HPES = Hypoparathyroidism Patient Experience Scale; LSM = least square mean

^aStatistically significant difference in LSM change, p<0.05.

The improvements in Hypoparathyroidism Patient Experience Scale (HPES) and generic 36-item Short Form Survey (SF-36) scores were sustained or improved to a similar level as observed in the palopegteriparatide group at week 52 in the open-label extension period of PaTHway.⁸

2.4. Supportive studies

PaTH Forward was a phase II study in patients with chronic hypoparathyroidism and had a 4-week randomised double-blind period followed by an open-label extension up to 266 weeks (n=59). Patients were randomised equally to receive palopegteriparatide at a starting dose of 15 micrograms, 18 micrograms and 21 micrograms daily or placebo, all patients received palopegteriparatide in the extension period. At week 214, 95% (56/59) of patients remained in the study, 93% of those had stopped conventional treatment and 98% had calcium levels within normal range. Mean eGFR was 86.0 mL/min/1.73² which was a mean increase of 7.6 mL/min/1.73² from baseline and mean 24-hour calcium levels normalised and remained ≤ 6.2 mmol/day. Mean bone turnover markers including CTx and P1NP were at the low end of normal at baseline and remained stable above baseline. Bone mineral density Z-scores trended towards normal but remained above zero. Additional data provided by the company at 5 years were consistent with results at week 214.^{11, 12}

3. Summary of Safety Evidence

Evidence from the PaTHway study supports the relative safety of palopegteriparatide compared with placebo for the treatment of chronic hypoparathyroidism. The placebo group, as a proxy for standard of care, is considered a relevant comparator in this submission. At week 26 the mean daily dose of palopegteriparatide was 21.5 micrograms.

At week 26, in the palopegteriparatide and placebo groups respectively, any treatment emergent adverse event (TEAE) was reported in 82% (50/61) and 100% (21/21), these were grade ≥ 3 in severity in 3.3% and 4.8% and led to treatment discontinuation in 1.6% and 9.5%. The most common TEAEs affecting $\geq 10\%$ in the palopegteriparatide group versus the placebo group were injection site reaction (31% versus 0%), headache (21% versus 9.5%), hypocalcaemia (9.8% versus 43%), fatigue (15% versus 24%), paraesthesia (18% versus 14%), muscle spasms (12% versus 14%) and nausea (12% versus 9.5%). At week 52 and 156 in the open-label extension study, the safety profile was similar to the 26-week blinded period in the palopegteriparatide group.^{6, 8, 9}

There was a greater reduction from baseline to week 26 in mean 24-hour urine calcium levels in the palopegteriparatide group compared with the placebo group and a higher proportion achieved normal 24-hour urine calcium excretion (≤ 250 mg per 24 hours). At weeks 52 and 156 in the open-label extension studies, mean 24-hour urine calcium excretion levels were within the normal range.^{6, 8, 9}

Treatment with palopegteriparatide has been associated with serious events of hypercalcaemia. The risk of hypercalcaemia is highest with treatment initiation and dose up-titration. This was reflected in the PaTHway study with the incidence of hypercalcaemia in the palopegteriparatide group highest in the first three months of treatment. The SPC provides further information on monitoring and dose adjustments based on serum calcium levels.¹

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Palopegteriparatide would be the first parathyroid hormone replacement therapy to be made routinely available in NHS Scotland for the treatment of chronic hypoparathyroidism.
- In the PaTHway study, a significantly greater proportion of patients achieved the composite primary outcome in the palopegteriparatide group compared with the placebo group (79% versus 4.8%) at 26 weeks. The results were described as statistically compelling and clinically relevant by the regulator. The open-label extension data from the PaTHway study and from the phase II PaTH Forward study support maintenance of treatment effect up to 156 weeks and 214 weeks respectively.^{2, 6, 8, 9, 11}
- Palopegteriparatide is a once daily subcutaneous injection that can be self-administered. Some patients may find this advantageous compared with the daily pill burden associated with conventional oral therapy.

4.2. Key uncertainties

- Active vitamin D doses were reduced by up to 50% at treatment initiation in all patients, with further dose adjustments in active vitamin D and calcium supplements at subsequent study visits based on serum calcium levels (dose reductions if normal or high calcium levels). Independence from vitamin D and therapeutic calcium was a component of the primary outcome too. If there were no attempts to reduce these then it would be unlikely patients in the control arm would achieve the primary outcome either. The Committee discussed the complexity of the study design but accepted that doses of conventional therapy would have stabilised by week 26.^{2, 4}
- Although statistically significant, the patient-reported quality of life results from PaTHway were potentially at risk of bias and should be interpreted cautiously. Reasons for potential bias include potential for unblinding of patients and investigators (patients were aware of calcium and vitamin D doses and substantial reductions were observed for patients taking palopegteriparatide) and the previously mentioned suboptimal standard of care treatment provided in the control group.²
- There is uncertainty regarding the effect of palopegteriparatide on clinically relevant, long-term treatment outcomes such as reduction in fracture risk, renal effects, and potential adverse drug reactions with chronic exposure to mPEG. However, it may be reassuring that reductions in 24-hour urine calcium to within normal levels were maintained over time (up to week 182 in PaTHway and up to 5 years in PaTH Forward), improvements in renal function were sustained and bone turnover markers and bone mineral density indicated a restoration of closer to normal bone physiology.^{2, 9-12}
- The submitting company has requested that SMC consider palopegteriparatide when positioned for use in patients with chronic hypoparathyroidism that are not adequately controlled on conventional therapy. Clinical experts consulted by SMC considered this proposed positioning to be appropriate. However, there is no universally accepted definition of “not adequately controlled”. The submitting company considered the Second International Workshop criteria were the most appropriate to define this subpopulation of the licensed indication and when applied to the PaTHway study, included the majority of patients in the ITT population at baseline. Some clinical experts consulted by SMC agreed with this definition while others indicated a narrower definition would be used such as criteria in the revised European Society of Endocrinology (ESE) guidelines.^{1, 4, 5}

[Other data were also assessed but remain confidential.*](#)

4.3. Clinical expert input

Clinical experts consulted by SMC considered that palopegteriparatide meets an unmet need and is a therapeutic advance for the subgroup of patients with chronic hypoparathyroidism who are not controlled on conventional therapy. They indicated that it would be used as a second line treatment in patients unable to achieve stable biochemistry results, have hypercalciuria, remain symptomatic or have poor quality of life despite optimised treatment with activated vitamin D and calcium supplements.

4.4. Service implications

There may be initial service implications and additional clinical resource required when initiating treatment as specialist clinicians will select eligible patients, and frequent monitoring of calcium levels is required to titrate to a maintenance dose. Patients will require education for self-administration and to recognise signs of hypocalcaemia and hypercalcaemia. However, the patient numbers are expected to be low and routine monitoring for hypoparathyroidism would recommence when the dose had been stabilised.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of palopegteriparatide, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Chronic hypoparathyroidism is a rare, lifelong condition that has a substantial impact on quality of life of the patient and their family. It can be challenging to maintain normal calcium levels and some patients continue to experience symptoms such as fatigue, numbness and brain-fog despite optimised conventional therapy. In severe forms, acute hypocalcaemia can be life threatening and is associated with neurological, neuromuscular and cardiac complications. These can be unpredictable and often require repeated hospital admissions. The condition can also cause long-term morbidity including chronic kidney disease, cataracts, cardiac disease and neuropsychiatric illness.
- PACE clinicians highlighted that chronic hypoparathyroidism is the only major endocrine deficiency in which the missing hormone is not routinely replaced. Patients rely on lifelong treatment with conventional therapy which includes oral calcium supplements and activated vitamin D analogues. These treat the biochemical deficit but do not restore the physiological actions of parathyroid hormone. The balance between managing calcium levels and avoiding long-term complications such as kidney stones and nephrocalcinosis can lead to suboptimal management. A small number of patients rely on regular hospital admissions for calcium infusions which can be painful and cause damage to veins and surrounding tissue. In patients who are not adequately controlled on conventional therapy, alternative effective treatment options are extremely limited. If available, palopegteriparatide would be the only licensed parathyroid hormone for the indication under review and therefore would fill a substantial unmet need.
- Palopegteriparatide treats the underlying hormone deficiency, maintaining serum calcium within range and urinary calcium at normal levels which improves symptom control and may reduce the risk of long-term complications. It is generally well tolerated with most side effects (such as hypercalcaemia or injection site reactions) mild or moderate in severity. The single daily subcutaneous injection may be more convenient and less disruptive to daily life compared with multiple tablets associated with conventional therapy or frequent intravenous infusions.

- Palopegteriparatide could have a positive impact on quality of life of patients and their family. Improved biochemical and symptom control would give patients the opportunity to maintain independence, continue employment and reduce the care burden on family and friends. Patients could continue to engage in family life, social activities and remain active. In patients with severe disease, regular hospital admissions for treatment and symptom management may no longer be required allowing a more normal life.
- There may be an initial increase in hospital visits as specialist endocrine input will be required to initiate treatment, titrate doses of palopegteriparatide and reduce conventional therapy and manage biochemical monitoring. However, once stabilised frequent monitoring is not required and resource use is likely to be reduced.
- PACE participants agreed the most appropriate place in treatment is as per the company proposed positioning in patients who are not adequately controlled using conventional therapy. Eligible patients are likely to be selected by endocrinologists who will initiate and manage treatment.

Additional Patient and Carer Involvement

We received a patient group submission from Parathyroid UK, which is a charitable unincorporated organisation. Parathyroid UK has received 50% pharmaceutical company funding in the past two years, including from the submitting company. A representative from the patient group participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The economic analysis is detailed in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis
Time horizon	Lifetime horizon, the modelled population stop at the age of 100 years.
Population	Adult patients with chronic hypoparathyroidism who are not adequately controlled (NAC) with conventional therapy (CT).
Comparators	The comparator of interest was CT, which consisted of oral administration of active vitamin D analogues with or without calcium.
Model description	A de-novo Markov model with three mutually exclusive health states: Adequately controlled (AC), NAC and Death.
Clinical data	The main source of clinical data was the PaTHway study. This supplied inputs for dosing up to Week 26, discontinuation and adverse events rates. A simplifying assumption was made that 100% of palopegteriparatide patients started the model in the AC health state. All patients receiving CT and those not meeting response criteria were classified as NAC and started in that health state. Additional inputs were drawn from the Clinical Practice Research Datalink (CPRD) database.
Extrapolation	The clinical outcomes were extrapolated over a lifetime horizon. For dosing, values up to week 26 from PaTHway are assumed to be constant thereafter.

	For discontinuation, rates from PaTHway open-label extension at week 156 were used to derive an exponential extrapolation for transitions from AC to NAC, supported by experts consulted by the company. For complications, incidences were sourced from CPRD database. State occupancy was held constant for patients who remained on palopegteriparatide. As such, the transition from AC to NAC was applied only for those patients discontinuing therapy, and patients who remained on treatment were assumed to maintain an AC state. Patients in the NAC state could not transition to AC.
Quality of life	EQ-5D-5L data was collected during the PaTHway study, and mapped to the EQ-5D-3L instrument to inform the health state utilities for the AC and NAC states. The values were age and gender adjusted. Complication and AE disutilities were taken from a range of sources.
Costs and resource use	Medicine costs include drug acquisition, drug administration and adverse even costs. Other costs included health state maintenance and end of life.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

The base case analysis indicated that palopegteriparatide was associated with both increased costs and increased health outcomes. Inclusive of the PAS discount, the incremental cost-effectiveness ratio was estimated at £47,999.

[Other data were also assessed but remain confidential.*](#)

Sensitivity analyses

A variety of scenarios were conducted to explore areas of uncertainty. The results of selected scenarios, inclusive of the PAS discount on palopegteriparatide, are presented in Table 6.2.

Table 6.2 Scenario Analysis Results (inclusive of PAS discount)

	Parameter	Base Case	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Base case			<i>CiC</i>	<i>CiC</i>	47,999
1	Dosing	Proportion of patients escalating dose fixed at week 26 and maintained thereafter	Proportion of patients escalating dose fixed at week 52 and maintained thereafter	<i>CiC</i>	<i>CiC</i>	65,648
2			Proportion of patients escalating dose fixed at week 104 and maintained thereafter	<i>CiC</i>	<i>CiC</i>	69,662
3			Proportion of patients escalating dose fixed at week 156 and maintained thereafter	<i>CiC</i>	<i>CiC</i>	74,524
4	Response rate	Economic model definition of response applied – Palopeg responders: 100% CT responders: 0%	PaTHway definition of response applied – Palopeg responders: 79% CT responders: 5%	<i>CiC</i>	<i>CiC</i>	58,000

5	Utility values	Values based on all patients	Values based on responder patients only	<i>CiC</i>	<i>CiC</i>	53,937
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Abbreviations: AC= adequately controlled; AE= adverse event; CT= conventional therapy; ICER = incremental cost effectiveness ratio; NAC= not adequately controlled Palopeg= palopegteriparatide; CiC = commercial in confidence

6.3. Key strengths

- Appropriate justification was provided for the comparator, time horizon, model structure and cycle length.
- Complications included in the model were identified through a combination of targeted literature review and validation by Scottish clinical experts.
- The PaTHway study provided a number of inputs used in the model, including dosing, discontinuation, AE rates and health state utilities.

6.4. Key uncertainties

The PaTHway study used a composite end point as its primary outcome, and response was defined based on patients achieving four criteria (listed in Table 2.1). Response in the economic model was defined differently, with the submitting company using a broader definition of AC. This introduced variation between the study and the economic model. While the submitting company provided some explanation for that value, it was not directly informed by study data, making it a source of uncertainty. The applied response rate had a potentially sizeable impact upon the economic results. Scenario 4, Table 6.2, applied the rate of response observed in the PaTHway study, although this is likely to be highly conservative.

- HRQoL data was collected during the PaTHway study and applied within the economics. Due to the nature of treatment, utility values may have been biased if patients and investigators were unblinded due to differing calcium and vitamin D requirements between the treatment arms.
- Dosing up to week 26 was taken from PaTHway and assumed constant thereafter. This assumption is supported by a German real world study of palopegteriparatide conducted by the submitting company, which showed low levels of dose escalation. However, rates of dose escalation observed in the open-label extension of the PaTHway study were higher, and use of those dosing levels substantially increase the ICER (Scenarios 1 to 3).

7. Conclusion

The Committee considered the benefits of palopegteriparatide in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as palopegteriparatide is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept palopegteriparatide for use in NHSScotland.

8. Guidelines and Protocols

Revised European Society of Endocrinology Clinical Practice Guideline: Treatment of Chronic Hypoparathyroidism in Adults was published in 2025.⁴

A European expert consensus statement on practical management of specific aspects of parathyroid disorders in adults and in pregnancy: recommendations of the ESE Educational Program of Parathyroid Disorders (PARAT 2021) was published in 2022.¹³

Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop were published in 2022.⁵

9. Additional Information

9.1. Product availability date

08 May 2026

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Palopegteriparatide	A starting dose of 18 micrograms once daily by subcutaneous injection with dose adjustments in 3 microgram increments based on serum calcium levels.	96,278

Costs from BNF online on 02 June 2026. Costs calculated based on a 21 micrograms once daily maintenance dose (the median dose from the PaTHway study). Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 273 patients eligible for treatment in year 1 and falling to 268 patients in year 3.

SMC is unable to publish the with-PAS budget impact due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 20 July 2026.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:* <https://www.scottishmedicines.org.uk/about-us/policies-publications/>

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC includes Scottish national contract prices in its decision-making. These contract prices are

commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document.

Patient Access Schemes (PAS): A PAS is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.