

## National Institute for Health and Care Excellence

**Health Technology Evaluation**  
**Palopegteriparatide for treating chronic hypoparathyroidism ID6380**  
**Response to stakeholder organisation comments on the draft remit and draft scope**

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

**Comment 1: the draft remit and proposed process**

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Ascendis Pharma	Ascendis considers Single Technology Appraisal to be an appropriate route for evaluating this topic.	Thank you for your comment.  No changes to the scope required.
	Parathyroid UK	This is an appropriate and very necessary evaluation of a required technology for the treatment of the rare condition of hypoparathyroidism. It is urgent for those patients to have a hormone replacement rather than poor symptom management with current treatment options.	Thank you for your comment.  No changes to the scope required.
Wording	Ascendis Pharma	Ascendis agrees that the wording of the draft remit appropriately reflects the issues of clinical and cost-effectiveness for the technology undergoing appraisal.	Thank you for your comment.  The remit wording in the scope has been changed to “appraise the clinical and cost-effectiveness of

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			palopegteriparatide within its marketing authorisation for treating chronic hypoparathyroidism.”
	Parathyroid UK	No comments.	No changes to the scope required.
Timing issues	Ascendis Pharma	<p>Currently, there is no commercially available treatment targeting the underlying cause of symptoms and complications due to chronic hypoparathyroidism (HPT). As a result, there is a high unmet need in patients with HPT.</p> <p>Current management of HPT patients consists of oral administration of calcium supplements, calcitriol or other active Vitamin D analogues. These treatments may alleviate symptoms but may produce a number of adverse effects that increase the burden of the disease, as calcium and Vitamin D supplementation does not address parathyroid hormone (PTH)-mediated effects.<sup>1</sup></p> <p>Although the short-acting PTH analogues teriparatide and abaloparatide (used in osteoporosis treatment) have occasionally (rarely) been used off-label for HPT, they do not maintain 24-hour physiological levels of PTH as is required for patients with HPT.</p> <p>The only currently licensed recombinant human PTH (rhPTH) therapy for HPT (rhPTH 1–84; Natpar®) is due to exit the global market by the end of 2024 due to unresolved manufacturing and supply issues with the product.<sup>2</sup></p> <p>1. Gafni RI, Collins MT. Hypoparathyroidism. Solomon CG, editor. N Engl J Med. 2019 May 2;380(18):1738–47.</p>	<p>Thank you for your comment. NICE has scheduled this topic into its work programme. For further details, please see the NICE website:  <a href="https://www.nice.org.uk/guidance/indevelopment/gid-ta11454">https://www.nice.org.uk/guidance/indevelopment/gid-ta11454</a></p> <p>No changes to the scope required.</p>

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		2. Astolfi D, Murphy D, Sanders B, Gulley L, Knoefler A, Park M, Tsao S, Mourya S, Rubin M. The Voices of Hypopara Survey: Journey of patients living with hypoparathyroidism [Internet]. Available from: <a href="https://ascendispharma.com/wp-content/uploads/2020/10/HP_Survey_Poster_2020_ASBMR.pdf">https://ascendispharma.com/wp-content/uploads/2020/10/HP_Survey_Poster_2020_ASBMR.pdf</a>	
	Parathyroid UK	Very urgent. Patients have been campaigning for PTH for 20 years and are living impaired lives because of its lack of availability.  This is costing the NHS more in emergency admissions and long term co morbidities associated with the lack PTH treatment.	Thank you for your comment. NICE has scheduled this topic into its work programme. For further details, please see the NICE website: <a href="https://www.nice.org.uk/guidance/indevelopment/gid-ta11454">https://www.nice.org.uk/guidance/indevelopment/gid-ta11454</a>  No changes to the scope required.
Additional comments on the draft remit	Ascendis Pharma	No comments	No changes to the scope required.
	Parathyroid UK	No comments	No changes to the scope required.

**Comment 2: the draft scope**

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Ascendis Pharma	<p><i>Ascendis proposes the following amended text:</i></p> <p>Hypoparathyroidism (HPT) is an endocrine disorder characterised by low or inadequate levels of endogenous parathyroid hormone (PTH). Deficiency of PTH, the principal regulator of calcium and phosphate homeostasis, can lead to complications including hypocalcaemia (low blood calcium levels), hyperphosphatemia (reduced renal excretion of phosphorus), renal dysfunction, kidney stones, cataracts, infection and cardiovascular events.<sup>3,4</sup> The most common symptoms of HPT include muscle cramps or pains, fatigue, paraesthesia (tingling) around the fingers, toes, and mouth, seizures, blurred vision, dry and rough skin, brittle nails, and neuromuscular irritability. There may also be symptoms related to the central nervous system such as inability to concentrate, memory loss or forgetfulness, depression and anxiety, which can have a significant impact on quality of life.<sup>5,6</sup></p> <p>HPT may be temporary or permanent depending on the cause. The condition commonly occurs after neck surgery, due to the removal of, or damage to, the parathyroid glands. HPT can also be due to a congenital, genetic, or idiopathic disorder which affects the function of the parathyroid glands, or due to radiation and mineral disposition.<sup>3</sup></p> <p>HPT is a rare condition with an estimated prevalence of 6 to 37 per 100,000 people.<sup>7,8</sup> Based on current population estimates, this equates to approximately 3,400 to 20,900 people in England.<sup>9</sup> Nearly a third of patients with HPT describe their condition as severe.<sup>10</sup> Post-surgical HPT is more common in females than males due to their increased risk of thyroid disease and the associated likelihood of undergoing thyroidectomy.<sup>8</sup></p> <p>The current standard of care for HPT consists of supplementation with oral calcium and Vitamin D analogues such as alfacalcidol or calcitriol to maintain adequate and stable calcium levels.<sup>11</sup> The focus of conventional treatment is to ameliorate symptoms, restore the serum calcium level to the normal range</p>	<p>Thank you for your comment.</p> <p>The background to the scope is intended to provide a short summary of the condition, its prognosis and epidemiology, and current standard care in the NHS.</p> <p>The scope has been amended to include further details of symptoms associated with the condition, epidemiology and current care.</p>

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		<p>and improve quality of life.<sup>6</sup> In cases of severe acute symptomatic hypocalcaemia, calcium may be given intravenously.<sup>11</sup> Calcium and phosphorus levels may also be managed by following a high-calcium, low-phosphorus diet.<sup>11</sup></p> <p>Patients with HPT are at risk for many long-term complications, resulting from the debilitating nature of the disease itself as well as from the adverse effects associated with conventional treatment regimens with oral calcium and active Vitamin D.<sup>12</sup> As a result, HPT adversely affects multiple organ systems, notably the kidney: patients with HPT have a three to six times higher risk of developing renal complications compared to the general population, and two times higher risk of developing end-stage renal disease (ESRD).<sup>13-15</sup></p> <p>References</p> <ol style="list-style-type: none"> <li>1. Gafni RI, Collins MT. Hypoparathyroidism. Solomon CG, editor. N Engl J Med. 2019 May 2;380(18):1738–47.</li> <li>2. Astolfi D, Murphy D, Sanders B, Gulley L, Knoefler A, Park M, Tsao S, Mourya S, Rubin M. The Voices of Hypopara Survey: Journey of patients living with hypoparathyroidism [Internet]. Available from: <a href="https://ascendispharma.com/wp-content/uploads/2020/10/HP_Survey_Poster_2020_ASBMR.pdf">https://ascendispharma.com/wp-content/uploads/2020/10/HP_Survey_Poster_2020_ASBMR.pdf</a></li> <li>3. Al-Sharefi A, Glenister E, Morris M, Quinton R. Is calcium supplementation always needed in patients with hypoparathyroidism? Clinical Endocrinology. 2019 Jun;90(6):775–80.</li> <li>4. Bilezikian JP, Brandi ML, Cusano NE, Mannstadt M, Rejnmark L, Rizzoli R, et al. Management of Hypoparathyroidism: Present and Future. J Clin Endocrinol Metab. 2016 Jun;101(6):2313–24.</li> <li>5. Bollerslev J, Rejnmark L, Marcocci C, Shoback DM, Sitges-Serra A, van Biesen W, et al. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol. 2015 Aug;173(2):G1-20.</li> </ol>	

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		<p>6. Hadker N, Egan J, Sanders J, Lagast H, Clarke BL. Understanding the Burden of Illness Associated with Hypoparathyroidism Reported Among Patients in the Paradox Study. <i>Endocrine Practice</i>. 2014 Jul;20(7):671–9.</p> <p>7. Astor MC, Løvås K, Debowska A, Eriksen EF, Evang JA, Fossum C, et al. Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway. <i>The Journal of Clinical Endocrinology &amp; Metabolism</i>. 2016 Aug;101(8):3045–53.</p> <p>8. Mannstadt M, Bilezikian JP, Thakker RV, Hannan FM, Clarke BL, Rejnmark L, et al. Hypoparathyroidism. <i>Nat Rev Dis Primers</i>. 2017 Aug 31;3(1):17055.</p> <p>9. Office for National Statistics. Population estimates for the UK, England, Wales, Scotland and Northern Ireland: mid-2021 [Internet]. [cited 2024 Mar 28]. Available from: <a href="https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2021">https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2021</a></p> <p>10. Hypopara.uk. Living with chronic hypoparathyroidism [Internet]. [cited 2024 Mar 28]. Available from: <a href="https://www.parathyroiduk.org/wp-content/uploads/2018/05/Living-with-chronic-hypoparathyroidism-final-report.pdf">https://www.parathyroiduk.org/wp-content/uploads/2018/05/Living-with-chronic-hypoparathyroidism-final-report.pdf</a></p> <p>11. Parathyroid UK. Current treatment [Internet]. [cited 2024 Mar 31]. Available from: <a href="https://parathyroiduk.org/hypoparathyroidism/current-treatment-of-hypopara/">https://parathyroiduk.org/hypoparathyroidism/current-treatment-of-hypopara/</a></p> <p>12. Khan AA, Rejnmark L, Rubin M, Schwarz P, Vokes T, Clarke B, et al. PaTH Forward: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial of TransCon PTH in Adult Hypoparathyroidism. <i>The Journal of Clinical Endocrinology &amp; Metabolism</i>. 2022 Jan 1;107(1):e372–85.</p> <p>13. Siggelkow H, Clarke BL, Germak J, Marelli C, Chen K, Dahl-Hansen H, et al. Burden of illness in not adequately controlled chronic hypoparathyroidism: Findings from a 13-country patient and caregiver survey. <i>Clinical Endocrinology</i>. 2020 Feb;92(2):159–68.</p>	

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		<p>14. Chronic Kidney Disease Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. <i>The Lancet</i>. 2010 Jun;375(9731):2073–81.</p> <p>15. Sundström J, Bodegard J, Bollmann A, Vervloet MG, Mark PB, Karasik A, et al. Prevalence, outcomes, and cost of chronic kidney disease in a contemporary population of 2·4 million patients from 11 countries: The CaReMe CKD study. <i>The Lancet Regional Health - Europe</i>. 2022 Sep;20:100438.</p> <p>16. Khan AA, Rubin MR, Schwarz P, Vokes T, Shoback DM, Gagnon C, et al. Efficacy and Safety of Parathyroid Hormone Replacement With TransCon PTH in Hypoparathyroidism: 26-Week Results From the Phase 3 PaTHway Trial. <i>J Bone Miner Res</i>. 2023 Jan;38(1):14–25.</p>	
	Parathyroid UK	<p>Background reads incomplete, it misses crucial details about the condition, the increasing prevalence, the impact of lack of treatment options and severely impacted quality of life.</p> <p>I have re-written and included more information and references.</p> <p>The parathyroid glands are situated in the neck in close proximity to the thyroid gland. They have an important endocrine function maintaining calcium and phosphate homeostasis in the body by the secretion of parathyroid hormone (parathormone PTH), which is responsible for this function<sup>1</sup>. When damage to, removal of, or genetic conditions or diseases impact this gland it can result in hypoparathyroidism, negatively impacting the tightly regulated control of calcium in the blood. ‘Calcium is the most abundant mineral in the human body where it has a structural role in bones and teeth and in the extracellular fluid where it regulates many processes including vascular tone, muscle contraction-dilation, nerve impulse transmission, intracellular signalling, ATP production, and hormone secretion’<sup>2</sup>.</p>	<p>Thank you for your comment.</p> <p>The background to the scope is intended to provide a short summary of the condition, its prognosis and epidemiology, and current standard care in the NHS.</p> <p>The scope has been amended to include further details of symptoms associated with the condition,</p>

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		<p>Hypoparathyroidism is a rare condition in which the parathyroid glands in the neck cannot produce enough or any parathyroid hormone (PTH) to provide vitamin D3 and to regulate the levels of calcium and phosphate in the blood. This leads to low blood calcium levels (hypocalcaemia) and raised blood phosphate levels (hyperphosphataemia). Symptoms of hypocalcaemia can be significantly debilitating due to the extent of the role that calcium has in the body's normal functions and includes numbness, confusion and tetany which develop along a spectrum ranging from mild to more severe, often with sudden onset and causing 'hypos' requiring emergency intravenous treatment via emergency department admission<sup>1</sup>.</p> <p>Some early signs of hypocalcaemia include fatigue, paraesthesia, slow/confused thinking, sensitivity to sound, shakiness, irritability, anxiety, diarrhoea, and gradually worsening muscle spasms. Without immediate treatment this may progress to severe muscle cramps, disorientation, and seizures<sup>3</sup>.</p> <p>It is directly associated with anxiety and depression, impaired quality of life<sup>2,3</sup>, cataracts and renal damage<sup>4</sup>. Hypoparathyroidism as a whole is associated with complications and comorbidities including severely impaired quality of life<sup>3</sup>, serious renal outcomes, and increased risk of depression<sup>2,3</sup>.</p> <p><b>Hypoparathyroidism is the only endocrine condition without a replacement hormone in the UK.</b></p> <p>Most cases of hypoparathyroidism are caused by accidental damage to or incidental removal of the 1 or more parathyroid glands following neck surgery<sup>1</sup> including thyroidectomy for cancer (post-surgical hypoparathyroidism) this results in transient or permanent hypoparathyroidism in 30% of cases<sup>1</sup>.</p> <p>It is predicted that the incidence of thyroid cancer will increase by 74% from 2014 to 2035 to 11 cases per 100,000 people by 2035<sup>5</sup>. Since the early 1990s, thyroid cancer incidence rates have increased by more than two-and-a-half times (175%) in the UK<sup>5</sup>. Rates in females have almost tripled (184%), and rates in males have increased by more than two-and-a-half times (173%)</p>	epidemiology and current care.



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		<p>(2016-2018)<sup>5</sup>. It is therefore likely that the incidence of hypoparathyroidism will also increase.</p> <p>Non-surgical forms may be congenital (occurring in the womb ) or acquired in childhood or later in life as an inherited and/or autoimmune condition or caused by radiotherapy or low magnesium levels<sup>6</sup>.</p> <p>Estimates of prevalence of hypoparathyroidism range between 6 and 37 per 100,000 people, which equates to between 3,400 and 20,900 people across England with hypoparathyroidism based on current population estimates<sup>7,8</sup>.</p> <p><b>Treatment</b></p> <p>Treatment for hypoparathyroidism is focused on attempted relief of symptoms.</p> <p>Current therapy (oral calcium supplements and active vitamin D analogues such as alfacalcidol or calcitriol) must be titrated to attempt to keep calcium levels stable and within the tight normal range. This is administered by the patient without any home monitoring of calcium in the blood. Calcium is taken orally 'as and when required' and uses 'guesswork' as to when and dose amount in an attempt to do the job of parathormone PTH.</p> <p>The activities of daily living and daily demands can cause rapid fluctuations in calcium causing distress to the patient managing the condition. Taking oral calcium does not provide immediate relief and the patient has to 'wait and see' before deciding to take another dose and 'wait and see' again. They may need to decide to go to the emergency department because their symptoms have not improved. Fluctuating symptoms are often a daily occurrence causing distress and anxiety. Where there are acute and severe symptoms of hypocalcaemia, calcium must be given intravenously in hospital.</p> <p>Many report a huge negative impact to their social life, work, relationships and mental health<sup>3</sup>. Many are not able to exercise regularly or at all due to the impact that has on calcium<sup>3</sup>, causing co morbidities<sup>3,4</sup>.</p>	

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		<p>The long-term calcium supplementation for hypoparathyroidism may affect kidney function, and has also been linked to a higher risk of cardiovascular disease<sup>4</sup>. Thiazide diuretics may be used. Treatment should aim to keep calcium levels high enough to avoid symptoms of hypocalcaemia but low enough to avoid kidney problems<sup>6</sup>.</p> <p>As a result of current treatment for hypoparathyroidism with vitamin D and calcium supplements, <b>hypercalcemia</b> can occur transiently but can be life-threatening. This results in high calcium levels in the blood (hypercalcaemia) and patients are at considerable risk of hypercalciuria (raised calcium levels in the urine) nephrolithiasis (kidney stones)and nephrocalcinosis (calcium deposits in the kidneys) with subsequent kidney damage and kidney failure<sup>4,6</sup></p> <p>Symptoms of high calcium (hypercalcaemia) include fatigue, stomach pain, migraines, disorientation, nausea and vomiting with risk of heart and kidney damage and cardiac arrest<sup>6</sup> without emergency treatment to reduce the calcium and balance potassium.</p> <p>In conclusion, current treatment remains unsatisfactory. In a study specifically looking at the burden of chronic hypoparathyroidism by Siggelkow et al ‘the majority of patients reported moderate to severe symptoms while receiving conventional therapy, and most reported treatment dissatisfaction’<sup>3</sup>. This study concluded that ‘the magnitude of symptom severity as reported by patients was inversely proportional to HRQoL and health status scores. Strikingly, the impact of chronic hypoparathyroidism on HRQoL was similar to or more pronounced than for other severe chronic diseases’<sup>3</sup>.</p> <p>References</p> <ol style="list-style-type: none"> <li>1. Rao SS, Rao H, Moinuddin Z, Rozario AP and Augustine T (2023) Preservation of parathyroid glands during thyroid and neck surgery Front. Endocrinol. 14:1173950. doi: 10.3389/fendo.2023.1173950</li> </ol>	

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		<ol style="list-style-type: none"> <li>2. Morelli, M.B., Santulli,G. and Gambardella, J (2020) Calcium supplements: Good for the bone, bad for the heart? A systematic updated appraisal. <i>Atherosclerosis</i>. 296:68-73.</li> <li>3. Siggelkow H, Clarke BL, Germak J, et al. Burden of illness in not adequately controlled chronic hypoparathyroidism: Findings from a 13-country patient and caregiver survey. <i>Clin Endocrinol (Oxf)</i>. 2020; 92: 159–168. <a href="https://doi.org/10.1111/cen.14128">https://doi.org/10.1111/cen.14128</a></li> <li>4. David K, Moyson C, Vanderschueren D, Decallonne B. Long-term complications in patients with chronic hypoparathyroidism: a cross-sectional study. <i>Eur J Endocrinol</i>. 2019;180:71-78</li> <li>5. Cancer Research UK, <a href="https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer#heading-Zero">https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer#heading-Zero</a>. Accessed April 2024.</li> <li>6. Parathyroid UK (2023). Hypoparathyroidism - Current treatment. Accessed February 2024</li> <li>7. NHS (2021). <a href="#">Hypoparathyroidism</a>. Accessed February 2024.</li> <li>8. Office for National Statistics (2022). Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2021. Accessed March 2024.</li> <li>9. Reid IR, Bolland MJ, Grey A, Does calcium supplementation increase cardiovascular risk? <i>Clin. Endocrinol</i> 73 (2010) 689–695</li> </ol>	
Population	Ascendis Pharma	Yes.	Thank you for your comment.  No changes to the scope required.
	Parathyroid UK	Yes.	Thank you for your comment.

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		If referring to prevalence in background (max 20,900) then possibly more. A comparable Danish study found 1 in 22,000. (Rejnmark 2015 JBMR) This Scottish survey found the prevalence of nonsurgical chronic hypoparathyroidism was greater than previously reported using a population-based approach.(Leese 2017 ASBMR) A Danish study found 1 in 27,000.	The estimates provided in the cited papers fall in the given range of between 6 and 37 cases per 100,000 people.  No changes to the scope required.
Subgroups	Ascendis Pharma	Subgroups based on eGFR and disease severity.	Thank you for your comment.  The scope has been amended to include eGFR and disease severity subgroups.
	Parathyroid UK	No.	Thank you for your comment.  No changes to the scope required.
Comparators	Ascendis Pharma	<p><i>Ascendis considers that the list of comparators should be as follows:</i></p> <ul style="list-style-type: none"> <li>• Established clinical management without palopegteriparatide, which may include: <ul style="list-style-type: none"> <li>• Vitamin D analogues such as alfacalcidol or calcitriol</li> <li>• Calcium supplements</li> </ul> </li> </ul>	Thank you for your comment.  Rescue therapies have not been added as relevant comparators since these would be used in an

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		<ul style="list-style-type: none"> <li>• Rescue therapies (emergency procedures performed at hospital when a patient suffers a calcium crisis):               <ul style="list-style-type: none"> <li>• IV calcium</li> <li>• Anti-epileptic drugs post-seizure</li> </ul> </li> </ul> <p><i>Regarding recombinant parathyroid hormone (PTH), the only currently licensed recombinant human PTH (rhPTH) therapy for HPT is Natpar<sup>®</sup> (rhPTH 1–84). Natpar<sup>®</sup> is due to exit the global market by the end of 2024 due to unresolved manufacturing and supply issues with the product,<sup>2</sup> and therefore Ascendis does not consider it an appropriate comparator.</i></p>	<p>acute/emergency setting, and the remit and population for the intervention focuses on management of chronic hypoparathyroidism.</p> <p>Recombinant human parathyroid hormone has been kept in the list of comparators – any potentially relevant comparators that are considered established NHS practice and available at the time of final scope sign off will be kept in the final scope.</p>
	Parathyroid UK	<p>No they are not all standard. They are generic; alfacalcidol and calcitriol do not provide adequate support the majority of people with hypoparathyroidism and it should be noted that access to all medications is becoming more difficult across the UK.</p> <p>Calcium supplements cause kidney damage and patients are often put on doses above the recommended low dose in an attempt to manage the symptoms of the condition. Aso standard are Vitamin D3 and magnesium supplements and thiazide diuretics. Kidney dialysis is the outcome for some patients</p>	<p>Thank you for your comment.</p> <p>Thiazide diuretics, magnesium supplements and teriparatide have been added to the list of relevant comparators.</p>

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		Recombinant parathyroid hormone, (teriparatide) is used by a very small minority of patients 'off label' and administered by injection or pump.	
Outcomes	Ascendis Pharma	<p><i>Ascendis considers that the outcome measures to be considered should be as follows:</i></p> <p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• Independence from conventional therapy<sup>1</sup></li> <li>• Reduction in calcium supplements and Vitamin D analogues</li> <li>• Serum calcium levels</li> <li>• Serum phosphate levels</li> <li>• Reduction in physical and cognitive symptoms</li> <li>• Health-related quality of life</li> <li>• Adverse effects of treatment</li> <li>• Healthcare resource utilisation (HCRU)</li> <li>• Renal function (eGFR)</li> <li>• CVD outcomes</li> </ul>	<p>Thank you for your comment.</p> <p>Outcome measures relating to changes in cognitive symptoms, renal function (eGFR) , cardiovascular outcomes and mortality have been added.</p>
	Parathyroid UK	<p>Yes</p> <p>However the following should be included;</p> <p>Better calcium stability ( fewer lows and highs)</p> <p>Urine calcium levels</p> <p>Fewer hospital admissions</p>	<p>Thank you for your comment.</p> <p>The list of outcomes has been amended to</p>

<sup>1</sup> Defined as a standing dose of active Vitamin D equal to zero and elemental calcium  $\leq 600$  mg.  
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		Include in the symptom reduction; fatigue, anxiety, depression scores, pain, brain fog.	include changes in cognitive symptoms, hospital admissions, calcium levels and mortality.
Equality	Ascendis Pharma	<p>Ascendis does not consider that the remit and scope need changing. However, it is expected that more women than men will be treated with palopegteriparatide; this is because post-surgical HPT is more common in women than men as women are more likely to have thyroid disease and hence undergo thyroidectomy.<sup>8</sup></p> <p>8. Mannstadt M, Bilezikian JP, Thakker RV, Hannan FM, Clarke BL, Rejnmark L, et al. Hypoparathyroidism. Nat Rev Dis Primers. 2017 Aug 31;3(1):17055.</p>	<p>Thank you for your comment.</p> <p>This has been added to the Equality Impact Assessment form issued along with the final scope.</p>
	Parathyroid UK	<p>Learning disabilities, communication difficulties, language.</p> <p>Difficulty as a rare condition group accessing expected patient pathways. Being pregnant may exclude patient from accessing treatment.</p>	<p>Thank you for your comment.</p> <p>This has been added to the Equality Impact Assessment form issued along with the final scope.</p>
Other considerations	Ascendis Pharma	None.	Thank you for your comment.

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			No changes to the scope required.
Questions for consultation	Ascendis Pharma	<p><i>Is recombinant parathyroid hormone currently in use in clinical practice in England for the treatment of hypoparathyroidism?</i></p> <p>The only currently licensed recombinant human PTH (rhPTH) therapy for HPT (rhPTH 1–84; Natpar®) is due to exit the global market by the end of 2024 due to unresolved manufacturing and supply issues with the product.<sup>2</sup></p> <p><i>Are there any particular symptoms of hypoparathyroidism for which a separate outcome related to reduction in symptoms should be listed?</i></p> <p>Renal function (eGFR) / kidney outcomes. Patients with HPT are at risk from the adverse effects associated with conventional treatment regimens with oral calcium and active Vitamin D.<sup>12</sup> Patients with HPT have a three to six times higher risk of developing renal complications compared to the general population, and two times higher risk of developing end-stage renal disease (ESRD).<sup>13–15</sup></p> <p>Outcomes related to physical and cognitive symptoms as measured by the Hypoparathyroid Patient Experience Scale (HPES).<sup>16</sup></p> <p><i>Where do you consider palopegteriparatide will fit into the existing care pathway for hypoparathyroidism?</i></p> <p>Palopegteriparatide will be prescribed for patients with HPT that are inadequately controlled on conventional therapy (calcium and Vitamin D supplements).</p>	<p>Thank you for your comment.</p> <p>Comments relating to comparators and outcomes are addressed above.</p> <p>No further changes to the scope required.</p>



		<p><i>Would palopegteriparatide be a candidate for managed access?</i></p> <p>No. Currently Ascendis believes that the data are complete and sufficient to enable a decision.</p> <p><i>Do you consider that the use of palopegteriparatide can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?</i></p> <ul style="list-style-type: none"> <li>• Reduction in pill burden. Managing HPT effectively often means that patients have a high number of pills to take every day – 27% take three to five pills every day.<sup>10</sup> More than a quarter of patients find the number of pills they are required to take challenging.<sup>10</sup> Moreover, managing blood calcium levels effectively can require patients to change the number of calcium pills and active Vitamin D capsules that they take daily: 21% of patients find the regular changes to the number of calcium pills to be challenging, and the figure is 16% of patients for active Vitamin D capsules.<sup>10</sup></li> <li>• Process disutility. As with other diseases with complex treatment pathways, HPT has a process utility associated with it.</li> <li>• Reduction in caregiver burden. Caregivers of patients with HPT experience considerable burden, including detrimental effects on their ability to work and perform daily activities.<sup>13</sup> Caregivers of patients with inadequately controlled HPT reported overall work impairment (20.8%) and negative impact on personal relationships (28% reported major impact on spousal/partner relationship).<sup>13</sup></li> </ul> <p><i>Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.</i></p> <p>Information on the topics listed above can be found in the cited references.</p> <p>References</p>	
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Section	Consultee/ Commentator	Comments [sic]	Action
	Parathyroid UK	<p><b>Questions for consultation</b></p> <p><b>Is recombinant parathyroid hormone currently in use in clinical practice in England for the treatment of hypoparathyroidism?</b></p> <p>Not routinely but Forsteo (teriparatide PTH 1-34) is available off label and in use by some patients.</p> <p><b>Are there any particular symptoms of hypoparathyroidism for which a separate outcome related to reduction in symptoms should be listed?</b></p> <p>Anxiety Urine calcium levels and kidney outcomes</p> <p><b>Where do you consider palopegteriparatide will fit into the existing care pathway for hypoparathyroidism?</b></p> <p>Currently care pathway is not meeting patient need. Ideally recommendation for PTH would be discussed on diagnosis as a routine treatment option.</p> <p><b>Would palopegteriparatide be a candidate for managed access?</b></p> <p>Yes, as there is no replacement hormone currently available for routine use.</p> <p><b>Do you consider that the use of palopegteriparatide can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?</b></p> <p>Yes, hypoparathyroidism is a rare condition so QALY may rate a drug lower and price it higher if its not providing full quality of life although improved quality of life will be seen as a considerable bonus to hypoparathyroidism patients.</p> <p><b>Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.</b></p>	<p>Thank you for your comment.</p> <p>Responses to consultation questions relating to comparators and outcomes have been addressed above.</p> <p>No further changes to the scope required.</p>

Section	Consultee/ Commentator	Comments [sic]	Action
		Standards of care for hypoparathyroidism in adults: a Canadian and International Consensus - Aliya A Khan et al, EJE Vol 190 Issue 3 p1-22 March 2019  Burden of illness in not adequately controlled chronic hypoparathyroidism: Findings from a 13-country patient and caregiver survey. Clinical Endocrinology Vol 92 Issue 2 Feb 2020. Heide Siggelkow, Bart L. Clarke, John Germak, Claudio Marelli, Kristina Chen, Helen Dahl-Hansen, Elizabeth Glenister, Nawal Bent-Ennakhil, Davneet Judge, Katie Mycock, Jens Bollerslev	
Additional comments on the draft scope	Ascendis Pharma	No comments	No changes to the scope required.
	Parathyroid UK	No comments	No changes to the scope required.

**The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope**

None