Record of the Endocrinology Advisory Committee Meeting held on 8 August 2022

This meeting was held virtually via Zoom

Endocrinology Advisory Committee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) Specialist Advisory Committees 2021.

Note that this document is not necessarily a complete record of the Endocrinology Advisory Committee meeting; only the relevant portions of the meeting record relating to Endocrinology Advisory Committee discussions about an Application or Pharmac staff proposal that contain a recommendation are generally published.

The Endocrinology Advisory Committee may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or Specialist Advisory Committees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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1. Attendance

Present	Apologies
Simon Wynn Thomas (Chair)	Bruce Small
Alistair Gunn	
Anna Fenton	
Bruce King	
Esko Wiltshire	
Stella Milsom	

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Somatropin for the treatment of adults and adolescents with Prader-Willi syndrome.	Medium Priority
• Somatropin for the treatment of short children born small for gestational age (SGA).	Medium Priority
• Somatropin for the treatment of short stature due to chronic renal insufficiency.	Medium Priority
• T3 containing treatments for hypothyroidism.	Decline

3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Endocrinology Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and Specialist Advisory Committees 2021, available on the Pharmac website at https://pharmac.govt.nz/assets/2021-Specialist-Advisory-Committee-Terms-of-Reference.pdf. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

3.3. The Endocrinology Advisory Committee is a Specialist Advisory Committee of Pharmac. The Endocrinology Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Endocrinology Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for endocrine conditions that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at

times, make recommendations for treatments for endocrine conditions that differ from the Endocrinology Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'. Pharmac considers the recommendations provided by both the Endocrinology Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for endocrine conditions.

4. Welcome and introduction

4.1. The Chair welcomed members to the meeting. Members and Pharmac staff introduced themselves. This meeting was held via zoom, for the Committee members and a combination of zoom and in-person for Pharmac staff.

5. Record of the previous Endocrinology Advisory Committee meeting

5.1. The Advisory Committee reviewed the minutes of the Endocrinology Subcommittee meeting held on Tuesday, 30 March 2021 and agreed that the minutes be accepted.

5.1.1. The Advisory Committee considered it would be beneficial in future to have a summary of outstanding funding applications for treatments for endocrine diseases within the record.

6. Review of PTAC records

6.1. The Committee reviewed the record of the August 2021 PTAC meeting, at which PTAC reviewed the record of the March 2021 Endocrinology Subcommittee meeting.

6.2. The Committee noted PTAC had considered explicit evidence relating to the denosumab Special Authority, oral bisphosphonates and renal impairment provided in the Endocrinology Subcommittee 30 March 2021 meeting record (link to published record).

6.2.1. The Committee considered that current evidence did not support the use of bisphosphonates in patients with impaired renal function. While bisphosphonates may be used in patients with impaired renal function, this goes against international best practice and the Committee considered it inappropriate to recommend a medicine that may exacerbate renal impairment. The Committee considered that the Special Authority criteria should have a reference to eGFR and that an eGFR of 35 ml/min aligns with the phase II trials for denosumab.

6.2.2. The Committee noted PTAC's view regarding patient persistence (link to published record) and considered that 50% of patients not taking oral bisphosphonates after three years likely reflected typical persistence in this therapeutic area, rather than specific intolerance.

6.3. The Committee noted PTAC's views regarding raloxifene and the recommendation to delist a medicine. The Committee considered there was limited use for raloxifene given its significant side effect profile, including risk of stroke, with limited benefit profile. Therefore, it was not widely used. The Committee considered that PTAC's

comments suggest they are looking to support clinical judgement and provide flexibility with the funded medicines.

6.4. The Committee noted PTAC's recommendation for cinacalcet for primary hyperparathyroidism.

6.4.1. The Committee considered that the proposed criteria were reasonable and that patient numbers were likely to be small. The Committee considered hospital admissions would be reduced, given the reduction in need for alternative management (i.e. IV fluids and IV bisphosphonates) and the proposal would have a significant benefit for people with primary hyperparathyroidism. The Committee highlighted the importance of considering hospitalisations for all three indications (primary, secondary and tertiary hyperparathyroidism) in the comparator for assessment.

6.4.2. The Committee was not aware of any new data for primary, secondary or tertiary hyperparathyroidism since PTAC's review, and re-iterated the importance of providing a treatment option for people who typically have no other funded options.

6.4.3. The Committee noted the application for cinacalcet for primary hyperparathyroidism was being actively progressed. The proposals for secondary and tertiary hyperparathyroidism were proposals which Pharmac wanted to fund, subject to available budget. However, these were not being actively progressed at the time of the meeting.

6.4.4. The Committee also noted that PTAC had highlighted in its meeting of August 2021 the uncertainty of patient numbers. The Committee considered that patient numbers would be expected to be low.

6.5. The Committee noted PTAC's recommendations for zoledronic acid for hypercalcaemia (May 2021), progesterone for menopause (August 2021) and testosterone gel (May 2022). The Committee noted the widening access to zoledronic acid, which is now funded for hypercalcaemia.

6.5.1. The Committee noted there had been several supply issues in the testosterone treatments subgroup, and testosterone gel would offer an additional presentation.

6.5.2. The Committee considered that gel may not be suitable for paediatric patients, as dose titration is challenging and potentially impossible. The Committee also considered it would need to be used with an occlusive dressing for very young paediatric patients, as they would often have physical contact with their caregivers. The Committee considered a gel product may be suitable for adolescents however considered the required dosing in this setting is often so

low that the gel may not offer a suitable funded option, particularly at the point of starting treatment.

6.5.3. The Committee considered that gel would be a good option for people receiving gender affirming hormone therapy.

7. Technology Assessment Report - Micronised progesterone for menopause

7.1. The Committee noted the Technology Assessment Report (TAR) for micronised progesterone for menopause.

7.2. The Committee noted updated dosing guidelines recommended that continuous progesterone, at a dose of 100 mg per day. The Committee considered this was common practice in New Zealand.

7.3. The Committee highlighted the importance of informing prescribers that dose adjustments of progesterone were required as oestrogen dosage increased.

7.4. The Committee noted the TAR is a technical document, however considered it useful to understand how clinical advice was utilised in Pharmac's processes.

8. Somatropin

Application

8.1. The Committee noted that Pharmac staff sought advice from the Committee regarding the funding restrictions for somatropin due to receiving specific comments from Committee members as follows:

8.1.1. Members indicated at the March 2021 meeting that the funding applications for adults and adolescents with Prader-Willi syndrome and short children born small for gestational age (SGA) should both be reviewed, in light of new systematic reviews.

8.1.2. Members also requested review of the glomerular filtration rates (GFR) within the restrictions for short stature due to chronic renal insufficiency.

8.2. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

8.3. The Committee **recommended** that the listing of somatropin in the Pharmaceutical Schedule be extended to the treatment of adults and adolescents with Prader-Willi syndrome with a **medium** priority, within the context of treatment of endocrine disease, subject to the following Special Authority criteria (changes in **bold** and ~~strikethrough~~):

Special Authority for Subsidy - Initial application
Prader-Willi Syndrome **(children)** – only from a paediatric endocrinologist or endocrinologist.
Approvals valid for 9 months for applications meeting the following criteria:
All of the following:

1. The patient has a diagnosis of Prader-Willi syndrome that has been confirmed by genetic testing or clinical scoring criteria; and
2. The patient is aged six months or older; and
3. A current bone age is < 14 years (female patients) or < 16 years (male patients); and
4. Sleep studies or overnight oximetry have been performed and there is no obstructive sleep disorder requiring treatment, or if an obstructive sleep disorder is found, it has been adequately treated under the care of a ~~paediatric~~ respiratory **or sleep** physician and/or ENT surgeon; and
5. Either:
   - 5.1 Both:
     - 5.1.1 The patient is aged two years or older; and
     - 5.1.2 There is no evidence of type 2 diabetes or uncontrolled obesity, as defined by BMI that has increased by greater than or equal to 0.5 standard deviations in the preceding 12 months; or
   - 5.2 Patient is aged between six months and two years and a thorough upper airway assessment is planned to be undertaken prior to treatment commencement and at six to 12 weeks following treatment initiation.

Renewal
Prader-Willi Syndrome **(children)** – only from a paediatric endocrinologist, endocrinologist **or practitioner on the recommendation of a paediatric endocrinologist or endocrinologist**.
Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Height velocity is greater than or equal to 50th percentile (adjusted for bone age/pubertal status if appropriate) as calculated over 6 to 12 months using the standards of Tanner and Davies (1985); and
2. Height velocity is greater than or equal to 2 cm per year as calculated over six months; and
3. A current bone age is 14 years or under (female patients) or 16 years or under (male patients); and
4. No serious adverse effect that the patient's specialist considers is likely to be attributable to growth hormone treatment has occurred; and
5. No malignancy has developed since growth hormone therapy was commenced; and
6. The patient has not developed type 2 diabetes or uncontrolled obesity, as defined by BMI that has increased by greater than or equal to 0.5 standard deviations in the preceding 12 months.

Special Authority for Subsidy - Initial application
Prader-Willi Syndrome (adults and adolescents) – only from a paediatric endocrinologist or endocrinologist. Approvals valid for 9 months for applications meeting the following criteria:
All of the following:

1. **The patient has a diagnosis of Prader-Willi syndrome that has been confirmed by genetic testing or clinical scoring criteria; and**
2. **A current bone age is 14 years or over (female patients) or 16 years or over (male patients); and**
3. **Sleep studies or overnight oximetry have been performed and there is no obstructive sleep disorder requiring treatment, or if an obstructive sleep disorder is found, it has been adequately treated under the care of a respiratory or sleep physician and/or ENT surgeon; and**
4. **There is no evidence of type 2 diabetes or uncontrolled obesity, as defined by BMI that has increased by greater than or equal to 0.5 standard deviations in the preceding 12 months.**

Renewal
Prader-Willi Syndrome (adults and adolescents) – only from a paediatric endocrinologist, endocrinologist or practitioner on the recommendation of a paediatric endocrinologist or endocrinologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. **No serious adverse effect that the patient's specialist considers is likely to be attributable to growth hormone treatment has occurred; and**
2. **No malignancy has developed since growth hormone therapy was commenced; and**
3. **The patient has not developed type 2 diabetes or uncontrolled obesity, as defined by BMI that has increased by greater than or equal to 0.5 standard deviations in the preceding 12 months.**

8.4. In making this recommendation, the Committee considered:

- The burden of disease on patients, caregivers and families from Prader-Willi syndrome
- That there is an unmet need due to a lack of effective alternative treatments
- That the cost of widening access to adults and adolescents would be low due to the small size of the patient group.

8.5. The Committee **recommended** that the listing of somatropin in the Pharmaceutical Schedule be extended to the treatment of short children born small for gestational age (SGA) with a current height two to three standard deviations below the mean with a **medium** priority, within the context of treatment of endocrine disease, subject to the following Special Authority criteria:

Special Authority for Subsidy - Initial application
Children born small for gestational age, with short stature and without growth hormone deficiency – only from a paediatric endocrinologist or endocrinologist. Approvals valid for 9 months for applications meeting the following criteria:

1. The patient's height is more than 2 standard deviations below the mean for age or for bone age if there is marked growth acceleration or delay; and
2. The patient was born small for gestational age and has not achieved catch-up growth by 2 years of age; and
3. Height velocity is <25th percentile for age (adjusted for bone age/pubertal status if appropriate), as calculated over 6 to 12 months using the standards of Tanner and Davies (1985); and
4. A current bone age is < 14 years or under (female patients) or < 16 years (male patients); and
5. The patient does not have severe chronic disease (including malignancy or recognised severe skeletal dysplasia) and is not receiving medications known to impair height velocity.

Renewal application – only from a paediatric endocrinologist or endocrinologist. Approvals valid for 12 months for applications meeting the following criteria:

1. Height velocity is greater than or equal to 50th percentile (adjusted for bone age/pubertal status if appropriate), as calculated over 6 to 12 months using the standards of Tanner and Davies (1985); and
2. Height velocity is greater than or equal to 2 cm per year as calculated over six months; and
3. A current bone age is < 14 years or under (female patients) or < 16 years (male patients).

8.6. In making this recommendation, the Committee considered:

- The increased cardiovascular risk in this population
- The unmet health need in terms of quality of life due to reduced height
- The height, body composition, and quality of life benefits of somatropin in this context, noting that cardiovascular benefits would not be expected.

8.7. The Committee **recommended** that the listing of somatropin in the Pharmaceutical Schedule be widened for the treatment of short stature due to chronic renal insufficiency with a **medium** priority, within the context of treatment of endocrine disease, subject to the following Special Authority criteria (changes in **bold** and ~~strikethrough~~):

Special Authority for Subsidy - Initial application
Short stature due to chronic renal insufficiency – only from a paediatric endocrinologist or ~~endocrinologist~~ **paediatric renal physician**. Approvals valid for 9 months for applications meeting the following criteria:
All of the following:

1. The patient's height is more than 2 standard deviations below the mean; and
2. Height velocity is <25th percentile for age (adjusted for bone age/pubertal status if appropriate), as calculated over 6 to 12 months using the standards of Tanner and Davies (1985); and
3. A current bone age is < 14 years or under (female patients) or < 16 years (male patients); and
4. The patient is metabolically stable, has no evidence of metabolic bone disease and absence of any other severe chronic disease; and
5. Either:
   5.1 The patient has a GFR less than or equal to ~~30~~ **60** ml/min/1.73m^2 as measured by the Schwartz method (Height(cm)/plasma creatinine (micromol/l) × 40 = corrected GFR (ml/min/1.73m^2) in a child who may or may not be receiving dialysis; or
   5.2 The patient has received a renal transplant and has received <5 mg/m^2/day of prednisone or equivalent for at least 6 months.

Renewal application – only from a paediatric endocrinologist or **paediatric** renal physician ~~on the recommendation of a paediatric endocrinologist or endocrinologist~~. Approvals valid for 12 months for applications meeting the following criteria:

1. Height velocity is greater than or equal to 50th percentile (adjusted for bone age/pubertal status if appropriate), as calculated over 6 to 12 months using the standards of Tanner and Davies (1985); and
2. Height velocity is greater than or equal to 2 cm per year as calculated over six months; and
3. A current bone age is 14 years or under (female patients) or 16 years or under (male patients); and
4. No serious adverse effect that the patients specialist considers is likely to be attributable to growth hormone has occurred; and
5. No malignancy has developed after growth hormone therapy was commenced; and
6. The patient has not experienced significant biochemical or metabolic deterioration confirmed by diagnostic results; and
7. The patient has not received renal transplantation since starting growth hormone treatment; and
8. If the patient requires transplantation, growth hormone prescription should cease before transplantation and a new application should be made after transplantation based on the above criteria.

8.8. In making this recommendation, the Committee considered:

- The burden of chronic renal insufficiency and associated growth impairment on patients, caregivers and families
- That there is an unmet need due to a lack of effective alternative treatments
- That the cost of widening access to those with GFR less than or equal to 60 mL/min/1.73m^2 would be low due to the small size of the patient group.

Discussion

Adults and adolescents with Prader-Willi syndrome

8.9. The Committee noted that the current funding of somatropin is for children with Prader-Willi syndrome (PWS) and considered that the lack of effective alternative treatments for adults and adolescents results in an unmet health need in this severe condition.

8.10. The Committee was made aware of evidence that very high mortality rates are observed in longitudinal registry studies of PWS, with mean age at death of 29.5 years and earlier death reported in males than in females (Butler et al. Genet Med. 2017;19:635-42; Manzardo et al. Genet Med. 2018;20:24-30). The Committee was made aware of evidence that mortality rates for individuals with PWS had decreased over time and considered that these decreases could be attributed to earlier detection and treatment of the condition, the increasing proportion of patients who are managed by multi-disciplinary care teams, an increased focus on weight management and diet, and access to growth hormone therapy for children with the condition. However, the Committee considered that there remains a significant early

mortality burden in PWS with a range of causes and that PWS conveys a high burden of disease.

8.11. The Committee considered there was no evidence of a difference in the incidence of PWS among Māori or Pacific peoples compared to other ethnicities. However, the Committee noted that inadequately managed PWS is associated with obesity, and considered that the burden of PWS for Māori and Pacific individuals with the disease and their families may be greater than non-Māori and non-Pacific people, given that the burden of obesity in New Zealand is greater among Māori and Pacific peoples compared to other ethnicities.

8.12. The Committee noted a systematic review of the use of growth hormone therapy in adults with PWS (364 unique patients) from 20 manuscripts that reported a variety of outcomes (Frixou et al., Clin Endocrinol (Oxf). 2021;94:645-655). The Committee considered that the patients included provided strong numbers for this rare condition and noted that the median age was 26.2 months with median follow-up of two years. The Committee noted that the authors reported a benefit on body composition, fat mass and muscle mass; some improvements in cardiovascular function in a limited number of studies; a variable impact on lipids; and no significant improvement in bone mineral density (although noting the data was short-term). The Committee considered that there was evidence from adolescent follow-up and cross-over studies that body composition worsens on cessation of growth hormone therapy. The Committee considered the studies provided very good safety data and showed a clear role of growth hormone therapy for improving body composition in the context of multidisciplinary care for PWS.

8.13. The Committee was made aware of evidence that was included in the meta-analysis by Frixou et al., from a randomised controlled trial including 46 adult participants (mean age 28 years) who received growth hormone or placebo for one year followed by growth hormone for two further years in all patients (Sode-Carlsen et al. J Clin Endocrinol Metab. 2010;95:4943-50). The Committee considered this trial provided data for a large number of patients with long follow-up. The authors reported improved body composition and improved respiratory function; the Committee considered the latter probably reflected muscle mass increase.

8.14. The Committee was made aware of small studies that reported growth hormone therapy over six months was associated with improved mental speed and flexibility and motor performance in 19 adults of median age 25 (Höybye et al. J Intellect Disabil Res. 2005;49:245-52), and that reported no difference in change in total, verbal or performance IQ during a year on growth hormone compared with a year on placebo in a two-year crossover study of 25 adults who had growth hormone therapy in childhood (Kuppens et al. 2016. Orphanet J Rare Dis. 2016;11:153). The Committee noted that participants in the latter study with a lower IQ at the start of the study lost more cognitive function during the year on placebo than in the year on growth hormone than those with a higher IQ at study start although IQ deterioration during placebo treatment was not significant overall, and that body composition deteriorated significantly while on placebo. The Committee considered this evidence used validated measures and suggested an impact of growth hormone on cognitive function. Members considered that changes in IQ in the range of 15 points would be

meaningful for patients and caregivers (eg from being intellectually disabled and requiring residential care to being within the normal IQ range and living at home).

8.15. Members were made aware of a one-year cohort study involving sequential MRI scans that reported an improvement in lean body mass, reduction in fat mass, improvement in overall balance and functional activity with growth hormone. Members considered this provided further support for the body composition benefits of somatropin (Casamitjana et al. J Clin Med. 2022;11:1831).

8.16. The Committee also noted the following evidence:

- Butler et al. Growth Horm IGF Res 2013;23:81-7
- Rosenberg et al., J Clin Endocrinol Metab. 2021;106:3068-3091
- Deal et al., J Clin Endocrinol Metab. 2013;98:E1072-87
- Backeljauw et al., Growth Horm IGF Res. 2021;57-58:101392
- Reus et al., Neurosci Biobehav Rev. 2012;36:1817-38

8.17. The Committee noted the challenges of conducting research in PWS included the rarity of the disease, meaning that large, randomised trials are not feasible, and childhood use of somatropin in most jurisdictions which makes conducting placebo-controlled trials unethical. The Committee considered that the evidence was of weak quality and likely confounded by socioeconomic and other factors.

8.18. Overall, the Committee considered that changes to lean body mass and body fat were the strongest surrogate outcomes associated with growth hormone treatment in PWS and noted that changes in body composition associated with growth hormone treatment in PWS were often not reflected in changes to body mass index (BMI). The Committee considered there was insufficient evidence of a difference in benefits or risks associated with growth hormone treatment in terms of cardiovascular risk or all-cause mortality, but that there was possibly a benefit in terms of cognitive function. On balance, the Committee considered that the evidence supported funding for somatropin use in adolescents and adults with the key outcome being improved body composition. The Committee considered that care by a multidisciplinary team appeared to be the most important influencing factor.

8.19. The Committee noted that a preliminary economic assessment of somatropin treatment for children with PWS had been carried out by Pharmac staff in 2006 (TAR 80 – Human growth hormone for children with PWS), and that somatropin was subsequently funded for this indication. The Committee considered that the estimated health-related quality of life impacts of PWS used in the 2006 analysis were not applicable to the adult PWS patient population but noted that the impacts of the condition spanned many domains of health-related quality of life and were generally of a moderate severity.

8.20. The Committee noted an estimate of the eligible population, if access to somatropin was widened for adults with PWS, of between 60 and 70 adult patients per year but considered this was likely an overestimate due to the high mortality rates associated

with PWS. The Committee considered that given the small population, the cost of widening access to somatropin in this population may be low.

8.21. The Committee considered that most patients would remain on somatropin treatment long-term, owing to the sustained treatment benefits observed and the favourable side effect profile. The Committee noted that discontinuations of treatment due to malignancies and other complications are uncommon.

8.22. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for somatropin if access were to be widened in New Zealand for adults and adolescents with PWS. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals with Prader-Willi syndrome who have reached skeletal maturity
Intervention	Somatropin, at a dose of 0.3 to 0.4mg per day Treatment assumed to be lifelong, provided the patient does not develop a malignancy, type II diabetes or uncontrolled obesity while on treatment.
Comparator(s) (NZ context)	No somatropin treatment
Outcome(s)	Improved body composition • Rosenberg et al. J Clin Endocrinol Metab. 2021;106: 3068-3091 reported that growth hormone treatment was associated with an increase in lean body mass of 1.95 kg (95% CI, 0.04 to 3.87 kg) and a reduction of fat mass of -2.23% (95% CI -4.10% to -0.36%) compared to placebo, among adults with Prader-Willi syndrome.

Table definitions:
Population: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup)
Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).
Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).
Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

Short children born small for gestational age (SGA)

8.23. The Committee noted that:

8.23.1. 2.3% of babies are born small for gestational age (SGA);

8.23.2. 80% of babies would experience catch-up growth within their first 6 months of life, with most completing this catch-up growth within two years;

8.23.3. babies born pre-term may take up to four years to complete catch-up growth;

8.23.4. one standard deviation (SD) is 7cm height for adult males and 6cm for females.

8.24. Overall, the Committee considered that between 8-10% of children would remain at a height two SD or greater below the mean throughout childhood, and that this represented the target population for this application. Members also considered that the health needs of this population would likely be similar to that of people with idiopathic short stature three SD below the mean, without growth hormone deficiency, who are eligible for funded somatropin.

8.25. The Committee considered the SGA patient group who would be eligible for somatropin treatment under the proposed amendments to the Special Authority would be small. The Committee noted that in Germany, where the access criteria were similar to those being proposed for New Zealand, roughly 12.1% of pre-term SGA children and 1.3% of full-term SGA children were reported to be eligible for growth hormone therapy (Olbertz et al. J Perinatal Med. 2019;47: 448-454).

8.26. The Committee noted that Māori are at an elevated risk of pre-term birth compared to other ethnicities, and as pre-term birth is a risk factor for being SGA, the burden of SGA with insufficient catch-up growth may be greater among Māori compared to non-Māori.

8.27. The Committee noted that SGA is associated with a range of poor long-term health outcomes including reduced levels of insulin-like growth factor-1 (IGF-1), insulin resistance, an increased risk of cardiovascular disease, and considered that there is some evidence of attenuated height gain during puberty.

8.28. The Committee considered that there is an unmet health need associated with conditions that result in short stature, although Members acknowledged this was predominantly derived from clinical experience and lower quality research outcomes (eg from small observational or qualitative studies) rather than high-quality clinical trial evidence for standard quality of life endpoints. The Committee noted that short stature has a considerable psychosocial impact on child and adolescent wellbeing, and problems such as bullying and social exclusion were often reported by both affected individuals and their whānau when presenting to endocrinologists. The Committee noted this impact was particularly severe for young males in adolescence. The Committee considered that impacts may also be seen in reduced relationship and employment success for males with short stature.

8.29. The Committee noted somatropin is funded in many jurisdictions and consequently, there is an absence of recent randomised clinical trials for this indication as placebo

controls would be unethical in this context. The Committee noted the following evidence for somatropin in children born SGA:

- Steen et al., Lancet Diabetes Endocrinol. 2017;5:106-116
- Loftus et al., J Pediatr Endocrinol Metab. 2010;23:535-51
- Backeljauw et al., Growth Horm IGF Res. 2021;57-58:101392
- Takeda et al., Health Technol Assess. 2010;14:1-209, iii-iv
- Christensen et al., Clin Ther. 2010;32:1068-82
- Christensen et al., J Med Econ. 2010;13:168-78

8.30. The Committee was made aware of the following evidence in children born SGA, most of which investigated low vs high dose growth hormone therapy:

- López-Siguero et al. Clin Endo. 2022;96: 558-568. The Committee noted that the authors of this single-arm, 10-year observational study reported gains in height (10cm extra) which the Committee considers were better than gains seen in idiopathic short stature, and that treatment did not lead to insulin resistance or excessive rise in IGF-1 levels.
- Lee et al. PlosOne. 2022;17: e0266329. The Committee noted that increases in height in 152 patients with SGA (48 prepubertal during treatment) were sustained over three years and the median patient had height well into the normal height range.
- Upners et al.JCEM. 2022;107: 2286-2295. The Committee noted that this prospective longitudinal multicentre study of 102 short children born SGA treated with growth hormone therapy reported no significant difference in treatment benefit for standard versus high dosages and that treatment response at one year was predictive of long-term treatment benefit. The Committee noted that boys (but not girls) in the treatment group had earlier onset puberty than in the reference group.
- Horikawa et al. Clin Pediatr Endocrinol. 2017;26: 63-72. The Committee noted that this multicentre, randomised, double-blind, parallel-group trial included 65 Japanese patients with height of less than 2.5 SDS and that mean age at treatment initiation was 5.3 years. The authors reported that, among patients who were treated with growth hormone, height at onset of puberty improved to -1.83 SDS for participants receiving the standard dose and -0.97 for high dose. Participants who received high-dose growth hormone had a greater mean bone age. The Committee considered that a treatment advantage associated with high-dose growth hormone would be expected to be attenuated by adulthood.
- Adler et al. Horm Res Paediatr. 2021;94: 52-62. The Committee considered that this retrospective cohort study of 252 patients with an average birth length of -2.0 ± 0.7 SDS who had achieved final height indicated that even patients initiated on growth hormone later would be expected to experience

improvements in final height, although the best responses to treatment were observed among patients who initiated treatment at younger ages.

- Quitmann et al. Frontr Pediatr. 2019;7: 164. The Committee noted that patients born SGA experienced improved health-related quality of life when treated with growth hormone versus untreated patients with idiopathic short stature after one year, although the Committee considered that the populations were not well matched for comparison.

- Boguszewski et al. J Clin Endocrinol Metab. 2020;105:dgaa203

- Labarta et al. J Pediatr Endocrinol Metab. 2020;33:923-32

8.31. The Committee considered that the evidence was of moderate quality and suggests somatropin is unlikely to improve long-term insulin resistance or reduce cardiovascular risk, however, it would be expected to increase height and body composition (improved lean muscle mass and reduced fat mass) and provide quality of life benefits to people born SGA due to these body composition benefits. The Committee noted considered that age of onset and adjusted prepubertal height influenced the benefit received and that this would likely be greater for the target group who were born SGA than for those currently able to access somatropin (ie those with height at least three SD below the mean) and greater than those with idiopathic short stature.

8.32. The Committee considered that it would be reasonable to target funding to children with current height of two to three SDS below the mean, equivalent to the second centile. The Committee considered that somatropin dosing in this context would use body surface area rather than bodyweight, although considered that 9.5kg was a reasonable estimate of weight for a one-year-old in the target group. The Committee noted there is variation in dosing internationally, however, considered that the lower dose of 1 mg/m^2 per day may be a preferred starting dose in New Zealand clinical practice (subsequently titrated up or down as needed according to both IGF-1 and growth responses), given that the higher dose of 2 mg/m^2 per day appears to provide only a marginal difference in effect compared with the lower dose.

8.33. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for somatropin if it were to be funded in New Zealand for the treatment of short children born SGA. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Children born small for gestational age (SGA) with height between 2 and 3 standard deviations below the mean for age.
Intervention	Somatropin, at a dosage of 1mg/m^2 to 2mg/m^2 per day • Age at treatment initiation assumed to be 2 years
Comparator(s) (NZ context)	No treatment
Outcome(s)	Accelerated growth rate, resulting in final height closer to normal range • Lee et al. PlosOne. 2022;17: e0266329 reported that children with SGA who received growth hormone treatment experienced an increase in height standard deviation score (HSDS) from a mean of-2.55 ± 0.49 before starting treatment to -1.13 ± 0.76 after 3 years of treatment (mean age treatment initiation 7 years). Attainment of greater final height extrapolated to assume an improvement in health-related quality of life • Christensen et al. Clin Endocrinol. 2007;67: 407-412 reported that adults with final heights closer to the normal range have better health-related quality of life (as measured by the EQ-5D) compared to adults with height standard deviation scores of ≤-2.0.
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

Children/adolescents with short stature due to chronic renal insufficiency

8.34. The Committee considered that chronic kidney disease (CKD) is associated with poor growth, and that the biological mechanism was understood to be a combination of low circulating insulin- like growth factor 1 (IGF1) levels and lower IGF-1 binding capacity due to renal insufficiency-related phycological impairments. The Committee noted that growth impairment is common among children with CKD, that poor growth is a marker of disease severity that is associated with significant morbidity and mortality, and that short stature impairs quality of life, self-esteem, and social rehabilitation (Drube et al., Nat Rev Nephrol. 2019;15:577-589).

8.35. The Committee noted that CKD disproportionately affects Māori, with growing evidence that there is a familial predisposition to CKD that is not due to diabetes (Walker et al. Semin Nephrol. 2019;39:297-99). The Committee also noted that there are difficulties in finding suitable kidney donors for Māori. Members considered

that this proposal would support a reduction in health outcome inequities for Māori for one complication of CKD in Māori children.

8.36. Members considered that Pacific children also have a higher incidence of CKD.

8.37. Members considered that chronic renal insufficiency is associated with a substantial health need and that the impact of short stature would be similar to that of idiopathic short stature.

8.38. The Committee noted that somatropin is funded subject to Special Authority criteria for the treatment of patients with short stature (height more than 2 standard deviations below the mean) due to chronic renal insufficiency according to criteria including GFR less than or equal to 30mL/min/1.73m^2 and considered that this is equivalent to CKD stage four (severe loss of kidney function) or five (kidney failure).

8.39. The Committee noted that international clinical practice recommendations for growth hormone treatment in children with CKD developed by members of the European Society for Paediatric Nephrology CKD–Mineral and Bone Disorder, Dialysis and Transplantation working groups recommend that children with stage three to five CKD or on dialysis should be candidates for growth hormone therapy if they have persistent growth failure, defined as a height below the third percentile for age and sex and a height velocity below the twenty-fifth percentile (Drube et al. 2019).

8.40. The Committee was made aware of evidence from several long term trials of growth hormone therapy in pre-pubertal children with chronic renal insufficiency that suggested a cumulative increase in height of 1.1–1.9 standard deviation score over five to six years (Fine et al. Kidney Int. 1996;49:781-5; Hokken-Koelega et al. Pediatr Nephrol. 2000;14:701-6).

8.41. The Committee also noted the following evidence:

- Loftus et al., J Pediatr Endocrinol Metab. 2010;23:535-51
- Al-Uzri et al., J Pediatr. 2013;163:736-41.e1
- Haffner et al., Pediatr Res. 1998;43:209-15
- Fine et al., J Pediatr. 2000;136:376-82
- Takeda et al., Health Technol Assess. 2010;14:1-209, iii-iv
- Mehls et al., Pediatr Nephrol. 2015;30:2145-51
- Youssef D M, Saudi J Kidney Dis Transpl. 2012;23:755-64

8.42. The Committee was made aware of evidence from a systemic review and meta-analysis of randomised controlled trials investigating whether growth hormone improved growth in paediatric renal transplant recipients which reported no significant differences in the rate of rejection episodes (risk ratio 1.56; 95% CI 0.97–

2.53) or eGFR between treatment groups (Wu et al. Pediatr. Nephrol. 2013;28:129–133).

8.43. The Committee noted evidence from a Cochrane meta-analysis of 16 randomised controlled trials that included 809 children aged zero to 18 years, diagnosed with CKD, who were pre-dialysis, on dialysis or post-transplant who received either growth hormone, placebo, or no additional treatment (Hodson et al. Cochrane Database Syst Rev. 2012:CD003264). The Committee considered that the main treatment benefits of somatropin after one year of treatment were an increase in height standard deviation score [mean difference (MD) 0.91; 95% CI 0.58–1.23] and increase in height velocity (MD 3.88 cm/y, 95% CI 3.32 to 4.44). The Committee noted that height velocity remained significantly greater in treated children than untreated children during the second year of therapy and considered that the estimated increase in adult height after two to five years of treatment could be about 7.4cm in boys and 7.0cm in girls. The Committee noted that a dose of 14 IU/m^2 per week (equivalent to 0.023 mg/kg per day) was associated with a higher increase in height velocity at one year compared with 28 IU/m^2 per week.

8.44. The Committee noted that the available evidence supported a treatment benefit in terms of accelerated growth rate spanning at least two years of treatment and had been observed in pre-pubertal children with various manifestations of renal insufficiency. The Committee considered it was reasonable to assume this treatment benefit would persist over a treatment duration of two to five years, resulting in final height closer to normal range. The Committee considered that there was evidence that somatropin treatment was safe in this population and that it would be expected to improve QOL through attainment of greater height, which would be associated with improved self-esteem (Christensen et al. Clin Endocrinol. 2007;67: 407-412). The Committee considered there was no evidence of a difference in benefits or risks associated with growth hormone treatment with regard to allograft rejection risk, decline in renal function, cardiovascular risk or all-cause mortality.

8.45. The Committee noted that this consideration was regarding widening of access of somatropin to children/adolescents with short stature due to chronic renal insufficiency with an eGFR of <40ml/min/1.73m^2. The Committee also noted that most international guidelines set the eGFR threshold for growth hormone eligibility at <60ml/min/1.73m^2 and that it was appropriate for the New Zealand Special Authority to be amended to align with these guidelines. The Committee considered that this widening access to children/adolescents with <60ml/min/1.73m^2 would not result in a substantial increase in patient numbers compared to the numbers currently observed at the 30ml/min/1.73m^2 threshold, as most children with impaired growth due to renal insufficiency would be among the currently funded patient group who have more advanced renal disease. The Committee considered that younger children with renal impairment would be considered for transplant rather than somatropin treatment.

8.46. The Committee noted that dosing of somatropin among children was usually calculated on a mg/m^2 basis compared to adult dosages, which were based on mg/kg. The Committee noted that the usual starting dose for somatropin in children with chronic renal insufficiency was 1mg/m^2/day, and that the dose could be increased to 1.4mg/m^2 per day for effect. The Committee considered that the

dosages reported in most trials and observational studies for somatropin in this indication were roughly equivalent to those used in New Zealand clinical practice.

8.47. The Committee considered that most children with chronic renal insufficiency were older children, and it was reasonable to assume an average age at treatment initiation of 8 years, and a body surface area of $1m^2$. The Committee considered that renal function of between 30 and 60 mL/min/$1.73m^2$ would remain relatively stable once treatment commences, although the length of time on treatment would vary depending on the underlying disease. The Committee therefore considered that the eligible patient group would increase over time. The Committee considered a very minor increase in resource usage may occur with annual bone age monitoring (usually to check predicted height) and IGF-1 testing twice per year (to check adherence and dosing), although noted that this population of children would routinely undergo blood testing every three or six months.

8.48. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for somatropin if it were to be funded in New Zealand for the treatment of short stature due to chronic renal insufficiency. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Children with short stature due to renal insufficiency and a GFR of 30 to 60ml/min/$1.73m^2$, who have a height lower than the 3^{rd} percentile.
Intervention	Somatropin - starting dose of $1mg/m^2$ per day and can be increased to up to $1.4mg/m^2$ per day • The average age of treatment initiation is assumed to be 8 years.
Comparator(s) (NZ context)	No growth hormone treatment
Outcome(s)	Accelerated growth rate, resulting in final height closer to normal range • Hodson et al. Cochrane Sys Rev. 2012;2 reported that one year of growth hormone treatment was associated with an increase in height standard deviation score of 0.82 (95% CI, 0.56 to 1.07) and increase in height velocity at six months of 2.85cm (95% CI, 2.22 to 3.48cm) compared to placebo, among children with chronic renal insufficiency. Treatment benefit is sustained for at least two years. Attainment of greater final height extrapolated to assume an improvement in health-related quality of life • Christensen et al. Clin Endocrinol. 2007;67: 407-412 reported that adults with final heights closer to the normal range have better health-related quality of life (as measured by the EQ-5D) compared to adults with height standard deviation scores of ≤-2.0

Table definitions:
Population: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup)
Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).
Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).
Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

9. T3 containing treatments for hypothyroidism

Application

8.49. The Committee reviewed the application from the Thyroid Association of New Zealand Incorporated for the use of T3 containing treatments for hypothyroidism.

8.50. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

8.51. The Committee recommended that T3 containing treatments for hypothyroidism be **declined**.

8.52. In making this recommendation, the Committee considered:

8.52.1. The evidence demonstrates that T3 containing treatments have no additional health benefit compared to T4 treatment alone in individuals with hypothyroidism.

8.52.2. The poor suitability of whole thyroid extract due to safety concerns regarding variation in biochemical responses between individuals and the risk of toxicity.

Discussion

Māori impact statement

8.53. No evidence was identified on the impact of funding T3 containing treatments for hypothyroidism on Māori health areas of focus or Māori health outcomes.

Background

8.54. The Committee noted that this funding application was reviewed by PTAC in November 2018 and recommended for decline. The Committee noted that, at this time, PTAC considered the overall quality of evidence was poor to moderate and that there was considerable uncertainty as to the possible effects of T3 containing treatments. It was noted that PTAC considered it was not possible to conclude that treatment with T3 met criteria for non-inferiority compared to standard treatment with levothyroxine (T4).

8.55. The Committee noted that additional information was received from the applicant in June 2019 and July 2021 addressing PTAC's rationale for decline. The Committee noted that the key points raised were that scientific opinion and literature does not support the view that all patients can adequately convert T4 to T3. The Committee

noted that this information also stated that there have been changes to several overseas therapeutic guidelines to include T3 containing treatments, including Europe and Italy, with liothyronine (a synthetic triiodothyronine, T3, treatment) funded through the NHS in the UK. It was also noted that the applicant stated there were issues with the design of the trials considered by PTAC in 2018, which have been highlighted by several Thyroid Associations overseas. The Committee noted the statements provided by the applicant from the British Thyroid Association and patients noting the benefits of prescribing T3 to the patient and health system.

Discussion

8.56. The Committee noted that hypothyroidism is a condition of the endocrine system in which the thyroid gland does not produce enough thyroid hormone. The Committee noted that hypothyroidism is caused by inadequate function of the gland itself (primary hypothyroidism), inadequate stimulation by thyroid-stimulating hormone from the pituitary gland (secondary hypothyroidism), or inadequate release of thyrotropin-releasing hormone from the brain's hypothalamus (tertiary hypothyroidism).

8.57. The Committee noted that the clinical manifestations of hypothyroidism are highly variable, depending upon the age at onset and the duration and severity of thyroid hormone deficiency.

8.58. The Committee considered the adverse impact of hypothyroidism on whānau as a result of caring for an unwell whānau member, however there was no evidence identified in this area.

8.59. The Committee considered that it is difficult to estimate the number of those with hypothyroidism, given the wide range in literature and inconsistent definitions. The Committee noted that some patient groups with clinical hypothyroidism report persistent symptoms on guideline based T4 replacement therapy. The Committee noted reports that 20% to 60% patients treated with T4 therapy express dissatisfaction according to studies on health-related quality of life (Perros et al. Thyroid. 2022 [preprint]). The Committee noted that that lethargy, low mood, and cognitive issues dominate the reported residual symptoms. The Committee noted that a wide variety of persistent unexplained symptoms are common in the general population and these overlap with the symptoms attributed to hypothyroidism. The Committee considered these are all nonspecific and poorly quantifiable parameters and that there is no conclusive evidence that these residual symptoms are linked to the underlying thyroid disease. It was noted that there are numerous anecdotes and case studies that describe individuals from this group who have symptomatic improvement on combination T3/T4 replacement. The Committee also noted suggestions that T4 monotherapy treatment delivers inadequate T3 at tissue level. Further, the Committee considered that there may be an active autoimmune process driving symptoms, and/or that the persistent symptoms are unrelated to thyroid disease.

8.60. The Committee noted that the T3 containing treatments included in the application (whole thyroid extract, normal and extended release T3 and synthetic T3/T4) are not approved by Medsafe for use in New Zealand. The Committee noted that the applicant advised that whole thyroid is currently available as a compounded

medicine, compounded on an individual, named patient basis, and that patients are currently self-funding this treatment in New Zealand.

8.61. The Committee noted that the dosing recommendations for thyroid treatments are determined by the laboratory findings and symptoms and adjusted accordingly. The Committee noted that dosage may vary from person to person and that a significant number of patients require lifelong treatment.

8.62. The Committee noted the supporting evidence from the applicant provided in its June 2019 and July 2021 responses to PTAC. The Committee noted that no new clinical trial evidence was presented by the applicant, and that there was no demonstrated benefit of combination therapy over isolated T4 therapy in the available trials. It was noted that the publications provided since 2018 were opinion pieces from four main protagonists for T3/T4 therapies with a focus on the inadequacies of the published randomised trials, the observation of a growth in utilisation of combination therapies (particularly in USA), extended evidence of benefit of T3/T4 therapy in rat models of hypothyroidism, and evidence around human genetic polymorphisms and other proposed mechanisms that may have a negative impact on T4 to T3 conversion.

8.63. The Committee noted the updated International Thyroid Society guidelines referenced by the applicant, which is summarised as follows:

8.64. British Thyroid Association (BTA) (December 2016): Reiterated the BTA executive committee's 2015 evidence-based position statement that while T4 therapy remains the standard of care, a carefully audited trial of T3 might be warranted in exceptional cases. Symptoms are not useful as a monitoring tool, reflecting the focus on biochemical monitoring of TSH and T4 to define treatment.

8.65. European Thyroid Journal (June 2012): T4 monotherapy remains the standard of hypothyroidism treatment. T4/T3 combination therapy might be considered as an experimental treatment modality.

8.66. Italian Society of Endocrinology and Italian Thyroid Association (July 2016): Position statement noting that recent clinical and experimental data supports the addition of T3 treatment in some selected hypothyroid patients when their symptoms persist, and their quality of life remains impaired despite adequate T4 monotherapy.

8.67. American Thyroid Association: Suggests there needs to be clinical trial format to the utilisation of combination therapy.

8.68. The Committee also considered the findings of a prospective, randomised, double-blind, crossover study of 75 hypothyroid patients randomly allocated to 1 of 3 treatment arms, levothyroxine (T4), levothyroxine (T4) plus liothyronine (T3) (and desiccated thyroid extract (DTE)),for 22 weeks. The Committee noted there were no differences for primary and secondary outcomes, except for a minor increase in heart rate caused by DTE. The Committee noted that outcomes were similar among hypothyroid patients taking DTE versus T3/T4 combined versus T4, however, that subgroup analyses of the 1/3 most symptomatic patients on T4 revealed strong preference for treatment containing T3, which improved performance on the 36-point thyroid symptom questionnaire, the 12-point quality of life general health

questionnaire, the Beck Depression Inventory, and the visual memory index (Shakir et al. J Clin Endocrinol Metab. 2021;106:e4400-13).

8.69. The Committee considered that the results from Shakir et al suggest there is no benefit of T3/T4 combination therapy over T4 alone. The Committee considered that if the proposed treatment group that would benefit from T3/T4 combination therapy (as suggested by the applicant) were accurate, then the randomised controlled data should have identified this. The Committee therefore considered the applicant's estimate of 16% of currently treated patients who would benefit from T3 containing treatment to be inaccurate. The Committee also considered the post-hoc analysis of this study to be of low quality given this subgroup included only 25 patients.

8.70. The Committee reviewed the information provided by the applicant regarding T3/T4 conversion rates. The Committee considered that, given T3 does not cross the blood-brain barrier, the biological plausibility of T3 impacting mood or cognitive symptoms is low. The Committee considered that there can be many factors which impact symptoms such as fatigue. The Committee noted that the only physiological difference observed in Shakir et al was transiently higher heart rate in the DTE group. This observation may provide some plausibility for the argument that symptoms of fatigue are a result of peripheral changes, however that tachycardia is not necessarily a beneficial outcome.

8.71. Members considered that the studies provided also noted difficulty in titrating T3 levels in participants, suggesting that T3/T4 combination treatment is unlikely to provide good control of symptoms given the differential effects of T3 and the variation between individuals. Members noted the lack of health practitioner resource and experience available for titration of T3 treatment increases the safety risks.

8.72. Members considered that there is evidence that some patients on T4 therapy are not receiving adequate response and these patients may benefit from T3 treatment. Members considered this group may be individuals with deiodinase issues, which is not easily diagnosed. However, it was considered that the number of individuals in this group is likely to be very small and much lower than the patient numbers estimated by the applicant, explaining why clinical trials have not identified a significant health benefit for T3 treatments to date.

8.73. Members considered the quality control of whole thyroid extract is unsatisfactory due to the variation in biochemical responses between individuals. It was considered that, given whole thyroid is only available as a compounded product in New Zealand, this further perpetuates the risk of dose inaccuracy and variability. Members also noted that whole thyroid extract is a porcine product and is therefore inappropriate for use in Jewish and Muslim individuals.

8.74. The Committee noted that there have been no updates to the cost and savings information for T3 containing treatments since the application was reviewed by PTAC in November 2018. The Committee considered that funding of T3 treatment could potentially increase healthcare expenditure via increased monitoring of T3 levels, repeat visits for titration and increased hospital admissions due to toxicity.

8.75. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information

for T3 containing treatment if they were to be funded in New Zealand for hypothyroidism. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Patients with hypothyroidism who have not received adequate benefit from T4 treatment or have a condition known to affect T4 to T3 conversion
Intervention	T3 containing treatments (whole thyroid extract, normal or extended release T3 or combination T3/T4) • Whole thyroid extract is initially administered at a dose of 15mg twice daily. The dose is adjusted every 2-3 weeks, depending on response, with a maintenance dose of 60mg twice daily. • Dosing for liothyronine for hypothyroidism is 25mcg once daily, adjusted by 25mcg every 1-2 weeks, with a maintenance dose of 25-75mcg daily • Dosing for T3/T4 (liotrix) is 6.25/25mcg (T4/T3) once daily, adjusted by 3.1/12.5mcg every 2-3 weeks, with a maintenance dose of 12.5/50-25/100mcg per day.
Comparator(s) (NZ context)	T4 (levothyroxine) administered at a dose of 50-100 mcg daily, adjusting by 25-50mcg every 3-4 weeks according to response, with a maintenance dose of 100-200mcg daily.
Outcome(s)	Limited or no health benefit, increased monitoring and potential hospitalisations Suggested reduction in symptoms associated with hypothyroidism, resulting in improved quality of life, but no quantifiable data to support this.

Table definitions:
Population: The target population for the pharmaceutical, including any population defining characteristics (eg Line of therapy, disease subgroup)
Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).
Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).
Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

9. Endocrinology Therapeutics summary and update

9.1. The Committee noted the information provided in the Endocrinology therapeutics summary and update paper.

9.2. The Committee considered that further detail regarding the outstanding funding applications would provide a useful context.

Calcium homeostasis

Cinacalcet

9.3. The funding proposal for cinacalcet for primary hyperparathyroidism was being actively progressed and was expected to be consulted on shortly. The Committee

reiterated the expected benefit to patients and the positive impact of this funding proposal.

Zoledronic acid 4 mg

9.4. The Committee acknowledged the positive decision to fund zoledronic acid for hypercalcaemia.

9.5. The Committee noted that the funding proposal to open list zoledronic acid (ie remove all restrictions) was being actively progressed and re-iterated its support for this proposal. The Committee noted that access to infusion services, particularly in community settings, remained a considerable issue and considered that Pharmac should work to remove these inequities.

Corticosteroids and related agents for systemic use

Prednisone/Prednisolone

9.6. The Committee noted that Pharmac had released a Request for Tenders for prednisolone tablets and a possible outcome of this process was that prednisolone tablets would be listed on the Pharmaceutical Schedule as an additional corticosteroid treatment option. The Committee considered that the majority of prednisolone prescribing would be in primary care and would cover multiple specialities, given its likely wide-ranging use. The Committee considered that all prescribers would benefit from information and support if prednisolone tablets were to be funded.

Methylprednisolone

9.7. The Committee considered prednisone and prednisolone tablets were both suitable funded alternatives for people receiving methylprednisolone tablets. The Committee noted that a wide range of corticosteroids were funded and that any of the oral steroids would be appropriate for individuals currently receiving methylprednisolone tablets.

9.8. The Committee noted that the tablet presentation was not widely prescribed and considered that there would not be any unmet health need if this presentation were to be delisted.

9.9. The Committee considered Pharmac should seek advice from neurologists and rheumatologists regarding the 40 mg per ml presentation for injection. The Committee considered there may be a possible unmet health need for paediatric patients if the 40 mg per ml injection presentation were no longer funded, as the 125 mg per ml (and other injection presentations) didn’t allow for the same dosing flexibility and titrating.

9.10. The Committee noted that there are four funded presentations of methylprednisolone injection (methylprednisolone as sodium succinate). The Committee considered that it may be appropriate to consolidate the market by delisting one or two of the currently funded injection presentations.

Sex Hormones Non-Contraceptive

Testosterone products

9.11. The Committee noted there were various topical and oral testosterone products used overseas that are not funded in New Zealand. The Committee noted that several groups, including older men and individuals undergoing gender-affirming hormone therapy, tend to prefer these formulations to injectable products. The Committee noted that the current patch products have usability issues, frequently requiring the use of multiple patches to achieve the desired dose, as well as common dermatitis reactions occurring with use of the patches.

9.12. The Committee considered that the tablets are preferred over patches as the primary non-injectable form of testosterone, due to ease of use and the ability to accurately titrate dose. As such, there was an ongoing health need.

Oestrogen Preparations

Oestradiol patches

9.13. The Committee considered that there are a small number of patients for whom the current patches do not provide sufficient transdermal oestrogen dosing, who would benefit from funded access to a greater number of patches. There are also some patients for whom the 100 mcg dose may not be sufficient, such as younger individuals, people undergoing gender-affirming hormone therapy and people who experience a sudden onset of menopause following anti-cancer treatment or surgery. In addition, for some individuals, the patches lose therapeutic effect which results in a requirement to replace the patch every 2 or 3 days. Some individuals find the patches do not stay attached, although the Committee reported that this was less common than having a shorter duration of therapeutic effect. The Committee highlighted that many of these groups are paying full cost for patches, when prescribed a dose higher than currently funded.

Ethinyloestradiol

9.14. The Committee noted that there are oestrogen gels available in many other countries, in sachet and pump form, as well as a spray. The Committee highlighted that some individuals are prescribed Oestrogel (an oestradiol gel prescribed under Section 29 of the Medicines Act 1981), and that this presentation is particularly useful for those who are allergic to patches or those using it as part of gender affirming therapy in adolescence. The Committee considered this would only be a small number of individuals.

9.15. The Committee noted that there were currently many supply issues. The Committee strongly considered that early, clear communication was vital in managing these issues, noting that Pharmac cannot control the manufacturing and supply chain problems themselves.

Other Progestogen Preparations

Progesterone

9.1. The Committee noted that Pharmac had completed consultation on the proposal to open list progesterone (i.e. remove all restrictions) and staff were now working through the responses. The Committee reiterated its support for this proposal.

Thyroid and Antithyroid Agents

Levothyroxine

9.2. The Committee noted that Pharmac had received a funding application for levothyroxine oral liquid. The Committee had previously indicated that the unmet health need would be for patients 0-12 months of age, given that they could be transitioned to oral tablets after this point, by crushing them into food.

9.3. The Committee considered the incidence of dosing errors for levothyroxine compounded oral liquids was difficult to establish. The Committee considered it would likely be low however was the risk was exacerbated by the use of differing compounding strengths in different parts of the country. The Committee considered that the impact of mis-dosing for an individual would be high. The Committee considered further review of the potential benefits of a proprietary levothyroxine oral liquid product would be useful. The Committee also considered moving to one standardised formulation would reduce the risk of dosing errors.

Trophic Hormones

Goserelin

9.4. The Committee noted that goserelin had been discussed at the previous meeting, and that there had been a manufacturing issue in early 2022. The Committee highlighted that there were ongoing issues with the currently funded brand of goserelin. Many individuals were needing to receive more frequent administration than expected due to the therapeutic effect wearing off prematurely, with some individuals requiring administration every 6 weeks, rather than the expected 12 weeks. The Committee also highlighted issues which had impacted the delivery of the goserelin implant, which may have been the result of manufacturing issues.

9.5. Members were made aware that an audit undertaken in Christchurch of people with pelvic pain and premenstrual dysphoric disorder (PMDD), that indicated about 90% of patients had to come back for more frequent administration prior to the recall, following which this dropped to about 60%. The Committee were made aware that, for some patients, this resulted in acute psychiatric care being needed when the therapeutic effect wore off early.

9.6. Members noted that some individuals prescribed leuprorelin (another GnRH analogue) also required more frequent dosing than expected. However, the Committee considered the proportion of patients requiring more frequent administration with Goserelin Teva was substantially higher than with the previous brand.

Somatropin

9.7. The Committee noted that the proposal to widen access to somatropin was considered separately at this meeting.

Vasopressin Agonists

Desmopressin acetate nasal drops

9.8. The Committee noted that desmopressin acetate nasal drops (Minirin) were discontinued in 2021 and that desmopressin wafers (Minirin Melt) were listed to address the unmet health need. The Committee indicated the funding of the wafers

had been well received by clinicians as well as individuals, caregivers and whānau. The Committee was not aware of any unmet health need following the discontinuation of nasal drops that had not been addressed by the funding of the wafer presentation.

Other Endocrine Agents

Cabergoline

9.9. The Committee noted bromocriptine was being discontinued by the supplier and that the Special Authority restrictions for cabergoline were amended to ensure patients could access a suitable funded alternative. Bromocriptine was due to be delisted on 1 September 2022.

9.10. The Committee noted that Pharmac had received correspondence from the New Zealand Society of Endocrinology, raising an issue about people who are intolerant to cabergoline and that Pharmac staff were currently exploring options to ensure these patients continue to have a suitable funded alternative.

9.11. The Committee was uncertain of the likely proportion of people who would be intolerant to cabergoline and have no suitable funded alternative. The Committee considered providing people with a choice of treatments would be preferable.

Danazol

9.12. The Committee noted that danazol was discontinued in 2021, with a small number of patients accessing funded stanozolol via the Named Patient Pharmaceutical Assessment pathway as an alternative. The Committee was not aware of any additional groups that had an unmet health need following the discontinuation of danazol.

Drugs Affecting Bone Metabolism

Denosumab

9.13. The Committee noted that Pharmac has assessed and ranked the proposals to widen access to denosumab following the Committee's recommendations in March 2021. The Committee re-iterated these proposals are a high priority within treatments of endocrine conditions and supported the progression of these proposals.

Zoledronic acid

9.1. The Committee noted that Pharmac has widened access to zoledronic acid 5 mg injections to include bone loss prevention post spinal cord injury.

9.2. The Committee noted that Pharmac is actively progressing the application to remove all restrictions for zoledronic acid, and that this would apply to both presentations; the 4 mg and the 5mg strength.

Teriparatide

9.3. The Committee noted that Pharmac intend to bring a paper to a future meeting on teriparatide as first-line treatment for vertebral fractures.

10. General feedback

10.1. The Committee discussed the process for appointments to and replacements on the Special Advisory Committee, noting the number of endocrinologists on the Committee was currently small. The Committee noted that there would be a Consumer representative in future meetings.

10.2. The Committee reiterated that the Named Patient Pharmaceutical Assessment pathway could be difficult to understand and that there appeared to be a 'grey area' between NPPA applications and Schedule funding applications. The Committee noted that products funded via the Pharmaceutical Schedule were usually expected to have Medsafe approval, and that Pharmac did not usually assess products until they had received such approval. This was dependent on suppliers being willing to submit their products for regulatory evaluation in New Zealand.