Endocrinology Subcommittee of PTAC
Meeting held 21 June 2016

(minutes for web publishing)

Endocrinology Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016*.

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

The Endocrinology Subcommittee 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.

These Subcommittee minutes were reviewed by PTAC at its meeting 3 & 4 November 2016, the record of which is available on the PHARMAC website.

Record of the Endocrinology Subcommittee of PTAC meeting held at PHARMAC on 21 June 2016

1 Cinacalcet

1.1 The Subcommittee reviewed the minutes from the Pharmacology and Therapeutics Advisory Committee (PTAC) meetings held in November 2015 and May 2016 in relation to cinacalcet and noted that PTAC had recommended that cinacalcet funding be declined for a number of indications including patients with primary, secondary and tertiary hyperparathyroidism.

1.2 The Subcommittee noted that PHARMAC had recently listed cinacalcet on the Pharmaceutical Schedule subject to Special Authority criteria for patients with parathyroid carcinoma or calciphylaxis and treatment-resistant hypercalcaemia, in line with PTAC's November 2015 recommendations.

1.3 The Subcommittee considered that there was a group of patients with an unmet clinical need who could benefit from cinacalcet, namely, those patients with primary hyperparathyroidism with symptomatic severe hypercalcaemia contraindicated to surgery, or where previous surgery had been unsuccessful. The Committee considered that the numbers would be relatively low, limited to a few patients per centre per year. The Committee noted that these patients have no alternative treatments.

1.4 The Subcommittee noted PTAC's view that there was a lack of evidence of benefit of cinacalcet for this patient group, particularly with respect to clinically meaningful outcomes. However, the Subcommittee considered that reduction of severe hypercalcaemia is a clinically meaningful outcome and that it would be reasonable to extrapolate the evidence for cinacalcet in patients with parathyroid carcinoma to this patient group.

1.5 The Subcommittee nominated [a clinician] to develop a submission supporting the use of cinacalcet in patients with primary hyperparathyroidism with symptomatic hypercalcaemia in whom surgery is contraindicated, or where previous surgery had been unsuccessful, for consideration by PTAC.

2 Micronised progesterone

2.1 The Subcommittee noted that an application for the funding of micronised progesterone (Utrogestan) had been resent to the February 2016 PTAC along with additional information. The Subcommittee noted the minutes from PTAC's February 2016 review. The Subcommittee noted PTAC's view that the data supplied was of weak strength and poor quality. However, some members disagreed with PTAC's review, conclusion and recommendation, noting that they considered that it was not possible, ethically, to conduct a blinded study.

2.2 The Subcommittee noted that carotid intima media thickness (CIMT) was a primary endpoint in the Early Versus Late Intervention Trial with Estradiol (ELITE) trial (Hodis et al. N Engl J Med 2016;374:1221-31), which was designed to assess the effects of early

versus late introduction of menopause hormone therapy (MHT) on cardiovascular disease (CVD) risk markers. Some members considered that CIMT is a well-accepted surrogate for CVD risk and, therefore, considered that the trial supported a reduction in CVD risk with the use of oral oestradiol plus micronised progesterone versus placebo when used early after menopause. The Subcommittee noted that another surrogate cardiovascular outcome, coronary artery atherosclerosis, assessed by CT imaging, was not different between groups.

2.3 The Subcommittee considered that observational data suggest a reduction in CVD and breast cancer risk from the use of micronised progesterone compared with synthetic progestogens from the large observational cohort E3N study, which had recently reported updated data on this finding (Dartois et al, Int J Cancer. 2016;138(10):2415-27). The Subcommittee also acknowledged that this research is necessarily hypothesis-generating.

2.4 The Subcommittee considered that there are observational data suggesting that micronised progesterone is a better option than synthetic progestogens, particularly for people who need treatment long-term (eg 20-30 years) such as young women and those with long-term severe symptoms, although there is a lack of high-quality evidence to support this claim. The Subcommittee noted that for the majority of women the length of symptoms is between four and eight years (mean duration eight years), whereas the breast cancer risk from synthetic progestogens increases after five to seven years.

2.5 The Subcommittee requested that PTAC re-reconsider its recommendation, particularly in light of the newly published data.

3 Denosumab

3.1 The Subcommittee noted PTAC's recent (May 2016) review of denosumab. The Subcommittee did not agree with PTAC's proposed criteria for denosumab, noting that there were particular advantages with denosumab, which can be used in patients with impaired renal function. The Subcommittee considered that denosumab would be also be appropriate for patients with severe reactions to zoledronic acid such that they were unable or unwilling to have further zoledronic acid infusions.

3.2 The Subcommittee considered that, as no treatment prevented all fractures, including a new fracture while on treatment as 'treatment failure' as part of the renewal criteria would be difficult to manage. Members considered that any restriction criteria could include patients who are intolerant to zoledronic acid. Members considered that it would be clinically appropriate to restrict prescribing to endocrinologists and rheumatologists.

3.3 The Subcommittee noted that while denosumab was an effective treatment, its effects wore off very rapidly when discontinued. Members noted that patients who had missed one of their 6-monthly doses might be prone to rebound vertebral fractures within months. The Subcommittee noted that this meant that denosumab would need to be taken long-term in patients that were unable to transition to other treatments after denosumab.

3.4 The Subcommittee **recommended** the following changes to the criteria for denosumab proposed by PTAC in May 2016 (additions in bold, deletions in strikethrough):

Initial application ~~from any relevant practitioner~~ **only from a relevant specialist**. Approvals valid without further renewal unless notified for applications meeting the following criteria:
All of the following:

1 The patient is a postmenopausal woman with severe, established osteoporosis; and
2 Any of the following:
  - 2.1 History of one significant osteoporotic fracture demonstrated radiologically and documented bone mineral density (BMD) ≥ 2.5 standard deviations below the mean normal value in young adults (i.e. T-Score ≤ -2.5) (see Note); or
  - 2.2 History of one significant osteoporotic fracture demonstrated radiologically, and either the patient is elderly, or densitometry scanning cannot be performed because of major logistical, technical or pathophysiological reasons. It is unlikely that this provision would apply to many patients under 75 years of age; or
  - 2.3 History of two significant osteoporotic fractures demonstrated radiologically; or
  - 2.4 Documented T-Score ≤ -3.0 (see Note); or
  - 2.5 A 10-year risk of hip fracture ≥ 3%, calculated using a published risk assessment algorithm (e.g. FRAX or Garvan) which incorporates BMD measurements (see Note); or
  - 2.6 Patient has had a Special Authority approval for alendronate (Underlying cause - Osteoporosis) or raloxifene; and
3 The patient has experienced at least one symptomatic new fracture after at least 12 months' continuous therapy with a funded antiresorptive agent at adequate doses (see Notes); and
4 **Either:**
  - **4.1 Patient has had a severe adverse reaction from zoledronic acid; or**
  - **4.2** Zoledronic acid is contraindicated because the patient's creatinine clearance is less than 35 mL/min; and
5 The patient must not receive concomitant treatment with any other funded antiresorptive agent for this condition or teriparatide.

Notes:

a) BMD (including BMD used to derive T-Score) must be measured using dual-energy x-ray absorptiometry (DXA). Quantitative ultrasound and quantitative computed tomography (QCT) are not acceptable.
b) Evidence suggests that patients aged 75 years and over who have a history of significant osteoporotic fracture demonstrated radiologically are very likely to have a T-Score ≤ -2.5 and, therefore, do not require BMD measurement for treatment with denosumab.
c) Osteoporotic fractures are the incident events for severe (established) osteoporosis and can be defined using the WHO definitions of osteoporosis and fragility fracture. The WHO defines severe (established) osteoporosis as a T-score below -2.5 with one or more associated fragility fractures. Fragility fractures are fractures that occur as a result of mechanical forces that would not ordinarily cause fracture (minimal trauma). The WHO has quantified this as forces equivalent to a fall from a standing height or less.
d) A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.
e) Antiresorptive agents and their adequate doses for the purposes of this Special Authority are defined as: risedronate sodium tab 35 mg once weekly; alendronate sodium tab 70 mg or tab 70 mg with cholecalciferol 5,600 iu once weekly; raloxifene hydrochloride tab 60 mg once daily. If an intolerance of a severity necessitating permanent treatment withdrawal develops during the use of one antiresorptive agent, an alternate antiresorptive agent must be trialled so that the patient achieves the minimum requirement of 12 months' continuous therapy

3.5 The Subcommittee considered that if the cost differential between the funded oral antiresportive agents and denosumab was minimal it would be reasonable to remove the requirement to trial an oral treatment prior to denosumab (ie criterion 3, above).

4 Alendronate with or without cholecalciferol

4.1 The Subcommittee noted that PHARMAC was considering running a competitive process for the supply of alendronate from mid 2018 (once patent NZ501807 has expired), and was seeking the Subcommittee's advice as to the need for a funded combination alendronate with cholecalciferol (vitamin D) product.

4.2 The Subcommittee noted that vitamin D is sometimes given prior to zoledronic acid because of the risk of severe hypocalcaemia from zoledronic acid in those with vitamin D deficiency. However, the Subcommittee considered that there was no evidence that routinely taking vitamin D with bisphosphonates improves clinically important outcomes versus bisphosphonates alone.

4.3 Therefore, the Subcommittee considered that there would be no clinical issues with the removal of a funded combination alendronate with cholecalciferol product. The Subcommittee noted that some prescribers may wish to co-prescribe vitamin D with alendronate if the combination product was delisted, and that this option would remain available for patients who were vitamin D deficient.

5 Zoledronic acid DXA scan requirement

5.1 The Subcommittee noted PTAC's May 2015 comment that access to dual-energy x-ray absorptiometry (DXA) scans is limited in some DHBs and incurs a cost in primary care, and that PTAC had requested that advice be sought from the Endocrinology Subcommittee as to whether the DXA-related criteria for alendronate, zoledronic acid, raloxifene and teriparatide remain appropriate.

5.2 The Subcommittee considered that there was no evidence that validated ultrasound bone "stiffness" as an effective diagnostic tool for bone density, and noted that computed tomography (CT) scanners required specific software with a specific cut-off which made it impractical for this use.

5.3 The Subcommittee considered that DXA remained an appropriate diagnostic tool and noted that not all the Special Authority criteria required a DXA scan.

5.4 The Subcommittee considered that there was no need to amend the criteria in relation to DXA scan requirements.

6 Somatropin for patients with Prader-Willi Syndrome

6.1 The Subcommittee noted that PHARMAC staff were seeking advice regarding the Special Authority criteria for somatropin in patients with Prader-Willi Syndrome (PWS); specifically with regards to patients under the age of two years and adults and adolescents with PWS with skeletal maturity as defined by a bone age >14 years (female patients) or >16 years (male patients).

Patients under the age of two years

6.2 The Subcommittee noted that PWS is a rare genetic disorder affecting three to four new patients per year in New Zealand. The Subcommittee noted that, as a group, patients with PWS have growth hormone deficiency but variable growth velocity. The Subcommittee considered that most patients with PWS would meet the current Special Authority criteria for somatropin at some point.

6.3 The Subcommittee considered that many parents of PWS patients wish to initiate treatment within the first 18 months following birth, which is not possible under the current Special Authority criteria which require a minimum of 6 months of height velocity assessments from the age of 12 months.

6.4 The Subcommittee noted that parents' main reason for wanting to start growth hormone early appeared to be the possibility that it might improve their child's strength and body mass index. The Subcommittee considered that the benefits of this would be to improve motor milestones, improve the ability to play with other children, and to improve long-term lean body mass (although the latter benefit is unproven).

6.5 The Subcommittee considered that the evidence for initiating treatment with growth hormone in the first 18-24 months following birth was weak. The Subcommittee noted the following studies:

- A non-randomised clinical study comparing growth hormone with coenzyme Q10 in 26 children aged one year, in which growth hormone had significantly greater effects on growth and body composition than coenzyme Q10 (Eiholzer et al. Am J Med Genet A. 2008;146A:873-80). The Subcommittee considered that the outcomes reported in the trial were as would be expected given the biology and treatments used, and noted that the results should be treated with caution given that the trial was not blinded or randomised.

- A study in 43 infants with PWS randomised to a growth hormone group (median age 2.3 years) or control group (median age 1.5 years), which reported that one year of growth hormone treatment significantly improved mental and motor development compared with controls (Festen et al. Clin Endocrinol (Oxf). 2008;68:919-25). The Subcommittee noted that these patients were over the age of two years.

- An uncontrolled study in 10 infants with PWS (mean age 1.0 year) which supported the role of growth hormone in improving short term growth in infants with PWS (Eiholzer et al. J Pediatr Endocrinol Metab. 2001;14 Suppl 6:1441-4).

6.6 The Subcommittee considered that the comparative trial in the under 2 year age group (Eiholzer et al. 2008) provided only very weak evidence for growth hormone improving cognitive function in infants, but noted that there was anecdotal evidence from parents of behavioural improvements.

6.7 The Subcommittee noted that although the evidence was weak, this was a very rare condition and there are inherent difficulties in conducting clinical trials in very young patients.

6.8 The Subcommittee considered that non-adherence to treatment was an ongoing issue for at least 30% of patients with PWS in New Zealand, which greatly reduces the effectiveness, and hence cost effectiveness, of this expensive treatment. As such, the Subcommittee considered that it was important to retain an appropriate measure of treatment efficacy and compliance in the renewal criteria. The Subcommittee noted that one potential option was using IGF-1 as a measure for adherence; however, members noted that IGF-1 would likely be normal or even elevated in obese PWS children at baseline and IGF-1 rises as age increases, which poses confounding difficulties in the assessment of the impact of somatropin on IGF-1. Members noted that 6-montlhly testing for IGF-1 would also be more invasive than height measurement. The Subcommittee considered that maintenance of normal growth velocity was the most reliable, objective and easiest to measure outcome for this purpose. The Subcommittee noted that normalisation of growth velocity remained the primary proven benefit of somatropin treatment.

6.9 The Subcommittee noted that explicitly funding somatropin for any other reason, such as improved lean body mass, could potentially result in a large amount of pressure to fund somatropin for a wide range of conditions where this was an issue, such as patients with other catabolic syndromes, rheumatoid arthritis and irritable bowel syndrome, which would be inappropriate on the basis of available evidence and taking into account the high cost of treatment.

6.10 The Subcommittee noted that in the past there had been a perception that growth hormone affected patients' appetite; however, members considered that this was unlikely as it does not readily cross the blood-brain barrier.

6.11 The Subcommittee considered that the evidence for an improvement in the quality of life for family and caregivers of PWS patients treated with somatropin was weak despite anecdotal evidence placing more emphasis on this. Members noted that the theory was that the more a child can do to help themselves then the less burden will be placed on the caregiver.

6.12 The Subcommittee noted that there were concerns regarding the relatively high prevalence of sleep apnoea in infants with PWS and the possible effect that growth hormone could have on tonsillar lymphoid tissue, potentially expanding adenotonsillar tissue bulk to cause additional airway obstruction. The Subcommittee noted that infants were more likely than older children to experience central sleep apnoea (43% versus 5%, respectively; Cohen et al. PLOS One 2014;9(6):e101012). The Subcommittee noted that there was no evidence that growth hormone affected sleep apnoea in young children; however, the risk of obstructive sleep apnoea was a significant and potentially life-threatening clinical concern. The Subcommittee considered that if access to somatropin for patients with PWS was widened to include patients under the age of two years, there should be a requirement for sleep monitoring or ENT assessment before starting treatment and at six to 12 weeks following treatment initiation.

6.13 The Subcommittee noted that there was no clinical trial evidence supporting the use of somatropin in patients with PWS below the age of six months. Given the lack of evidence and the potential risks, the Subcommittee was not supportive of widening access to growth hormone for patients with PWS below the age of six months.

6.14 The Subcommittee considered that the PHARMAC estimates of the number of children with PWS aged under two years in New Zealand, and the likely dose they would take, were reasonable.

6.15 The Subcommittee **recommended** that the initial Special Authority criteria for somatropin be widened to include treatment of patients with PWS over the age of six months as follows (additions in bold, deletions in strikethrough), with no changes to the current renewal criteria, with a medium priority:

Initial application — (Prader-Willi syndrome) 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's height velocity is < 25th 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~~

~~3 Either:~~

~~3.1 The patient is under two years of age and height velocity has been assessed over a minimum six month period from the age of 12 months, with at least three supine length measurements over this period demonstrating clear and consistent evidence of linear growth failure (with height velocity < 25th percentile); or~~

~~3.2 The patient is aged two years or older; 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 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 II diabetes or uncontrolled obesity defined by BMI that has increased by ≥ 0.5 standard deviations in the preceding 12 months; **or**

5.2 The patient is aged between six months and two years and thorough ENT assessment for airway obstruction is planned to be undertaken prior to treatment commencement and at six to 12 weeks following treatment initiation.

6.16 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework for this recommendation.

Adults

6.17 The Subcommittee considered that the PHARMAC estimates of the number of adults with PWS in New Zealand, and the likely dose they would take, were reasonable.

6.18 The Subcommittee considered that the evidence base for the use of somatropin in adults with PWS was even weaker than for patients aged under two years.

6.19 The Subcommittee noted that the published literature in adults with PWS does not support a reduction in body mass index (BMI) from starting growth hormone, and there is no evidence that stopping growth hormone in adults with PWS increases BMI. The Subcommittee noted that there was one small published study that suggested that stopping growth hormone increased body mass but not BMI (Butler et al. Growth Horm IGF Res 2013;23:81-7).

6.20 The Subcommittee considered that the main benefit of somatropin in adults with PWS was likely to be improved strength and mobility in the short term, but the longer term clinical benefit was unclear.

6.21 Similarly, the Subcommittee considered that there was insufficient evidence to support a quality of life benefit from somatropin in these patients.

6.22 On the basis of lack of evidence for clinically meaningful long-term benefit, the Subcommittee **recommended** that the application to widen access to somatropin to include treatment of adults and adolescents with PWS with skeletal maturity as defined by a bone age >14 years (female patients) or >16 years (male patients). adults be declined.