Growth Hormone Subcommittee of PTAC meeting held 20 October 2009

(minutes for web publishing)

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Note that this document is not necessarily a complete record of the Growth Hormone Subcommittee meeting; under the Terms of Reference, only the relevant portions of the minutes relating to Growth Hormone Subcommittee discussions about applications that contain a recommendation are generally published.

The Growth Hormone 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.

Contents

1 Review of PWS criteria

1.1 The Subcommittee discussed the rationale for growth hormone treatment in children with Prader-Willi Syndrome (PWS). Members noted that patients with PWS had a hypothalamic defect that resulted in some patients having reduced growth hormone secretion, but growth hormone levels were difficult to measure in these patients. Members noted that when funding for this indication was approved, height and height velocity were included in the criteria as additional measures of growth hormone sufficiency.

1.2 The Subcommittee noted that although the evidence for targeting treatment to patients growing poorly was lacking, the inclusion of measures such as poor height velocity in the criteria was an acceptable compromise between the difficulties of growth hormone stimulation testing and the need for objective measures in this patient group.

1.3 The Subcommittee discussed whether there was any evidence of unmet need in this patient population and considered that there was no evidence that patients in need were being declined treatment. Members considered that the issue of inequity had been considered previously by the Subcommittee and that the removal of the requirement for patients to have a height less than the 3rd percentile addressed the previous inequity.

1.4 The Subcommittee discussed whether the criteria may be biased against individuals who have obesity driven height gain. Members considered that the effects of growth hormone on body composition would be limited in obese patients who did not have adequate control over their diet prior to growth hormone being initiated. Members noted that the evidence was stronger for growth hormone improving lean muscle mass than reducing fat mass.

1.5 Members noted that DEXA scanning was not being routinely performed in patients with PWS and noted that this is a difficult test to perform in children under five years of age.

1.6 The Subcommittee considered that removing the height velocity criterion from the criteria would not incur significant expenditure, as the number of patients affected would be small, but considered that it would represent a major paradigm shift. Members considered that if this criterion were to be removed, growth hormone would be then subsidised for improvement of body composition rather than treating growth hormone deficiency (GHD). Members considered that the evidence was stronger for the growth promoting effects of growth hormone than for improvements in body composition and that this evidence was utilised in PHARMAC's original cost-utility analysis. Members noted that improved body composition is one benefit of treatment in adults with severe GHD, but considered that those individuals were severely affected by GHD and this was one of several domains that treatment with growth hormone aims to improve.

1.7 The Subcommittee briefly discussed growth hormone treatment in adults with PWS but considered that evidence for treatment in this group was lacking. Members considered that further studies were likely to be published demonstrating the effects of growth hormone on long-term outcomes in adults with PWS.

1.8 The Subcommittee did not consider that a change in the approach to funding in Australia should be considered when making recommendations on funding in New Zealand. Members considered that in the absence of any new evidence, there was no justification to recommend any changes to the criteria.

1.9 The Subcommittee **recommended** that the requirement for patients to have a growth velocity less than the 25th percentile be retained in the criteria.

2 Review of criteria for adults with growth hormone deficiency

2.1 The Subcommittee considered that the Assessment of Growth Hormone Deficiency in Adults (AGHDA) questionnaire was, for adult patients, the most appropriate tool for measuring impairment in quality of life resulting from growth hormone deficiency and for quantifying response to growth hormone therapy. The Subcommittee considered that an AGDHA score is quick and easy to measure and is well validated in this patient population.

2.2 The Subcommittee discussed whether other objective measures could also be incorporated into the criteria. Members considered that although other measures such as body composition, bone density and lipid profiles would be expected to improve with growth hormone treatment, these would be difficult to interpret. The Subcommittee noted that the National Institute of Clinical Excellence (NICE) had reviewed the effects of growth hormone treatment on other domains but that its recommendations had settled on AGHDA score as the best available tool for measuring treatment efficacy.

2.3 The Subcommittee considered that an improvement in quality of life, as quantified by an improved AGHDA score, would likely capture improvements in these other domains. However, members considered that it would be possible for patients to report an improvement in quality of life despite a lack of improvement in any other domains and that there was no objective way to challenge this.

2.4 The Subcommittee considered that an AGHDA score of greater than or equal to 16 is a strict entry criterion but noted the NICE data indicating a large treatment benefit in patients with a baseline AGHDA score of greater than 15. The Subcommittee noted that the UK recommends treatment in individuals with an AGHDA score of greater than or equal to 11.

2.5 The Subcommittee noted that patients who respond to treatment would show a response soon after treatment is initiated. The Subcommittee considered that as growth hormone is an injectable treatment, the patients most likely to continue with treatment would be those who had a significant improvement in quality of life, although members noted that there would be some patients who would continue with treatment even if there was no perceived benefit.

2.6 The Subcommittee discussed compliance monitoring in patients and noted that non-compliant patients may have their dose increased inappropriately in response to a low IGF-1 result. Members considered that such patients would not be likely to continue with treatment in the long-term as if their IGF-1 result remained low despite treatment at the ceiling dose, growth hormone supply would be stopped. Members considered that a vial exchange program would be an extremely useful tool to monitor compliance.

2.7 The Subcommittee considered that a number of patients with multiple pituitary hormone deficiencies would have IGF-1 values in the low/normal – normal range. The Subcommittee **recommended** that the IGF-1 criterion be revised from more than two standard deviation scores (SDS) below the mean to more than one SDS below the mean.

2.8 The subcommittee **recommended** the following criteria (changes to criteria proposed in 2007 shown in bold):

Entry Criteria:

- the presence of a medical condition known to cause growth hormone deficiency (e.g. surgical removal of the pituitary for treatment of a pituitary tumour); and
- appropriate treatment of other hormonal deficiencies and psychological illnesses; and
- severe growth hormone deficiency defined as a peak serum GH level ≤ 3µg/l (9mU/l) during an adequately performed insulin tolerance test or cross-validated equivalent test. In patients with multiple pituitary deficiencies one test would be sufficient. In patients with no other anterior pituitary deficiency two growth hormone stimulated tests should be performed; and
- serum IGF-1 more than **1 SD** below the mean for age and sex; and
- poor quality of life as defined by a score of ≥ 16 using the disease-specific quality of life questionnaire for adult growth hormone deficiency (QoL-AGHDA)**.**

Exit criteria:

- Major adverse effects of treatment.
- Patient preference not to continue treatment.

- Failure to reach or maintain serum IGF-I levels within 1SD of the mean normal value for age and sex despite the use of ceiling doses of growth hormone (0.7mg/day in males, 1mg/day in females).

- Failure to improve >7 points on the QoL-AGHDA score from baseline.

- Once stable on growth hormone treatment, a deterioration in the QoL-AGHDA score by >5 points unrelated to obvious external factors on 2 measurements >6 months apart.

- Unsatisfactory follow-up or compliance.

2.9 The Subcommittee considered that the variability of IGF-1 and growth hormone assays across the country was a problem. This may disadvantage patients in some areas of the country. The Subcommittee considered that further discussion with laboratories would be required to standardise testing across the country.

2.10 The Subcommittee discussed whether patients with multiple pituitary hormone deficiencies and a low IGF-1 should be required to undergo growth hormone provocation testing. Members considered that this would be appropriate, but noted that this requirement should be reviewed in the future. Members considered that the insulin tolerance test and glucagon were the preferred growth hormone provocation tests.

2.11 The Subcommittee discussed whether patients who were already self-funding treatment would be required to undergo a further assessment, including growth hormone provocation tests, before applying for growth hormone therapy. PHARMAC staff noted that such patients would be assessed by PHARMAC on a case-by-case basis, and if they would have met the criteria prior to starting self-funded treatment, it is likely that they would be eligible for ongoing treatment without being required to undergo further tests.

2.12 The Subcommittee **recommended** that the starting dose of growth hormone be 0.2 mg daily and noted that a lower starting dose was associated with a reduction in side effects. Members considered that growth hormone dose should be titrated at one month intervals for the first three months followed by a six month maintenance period. Members noted that the ceiling dose may be higher in premenopausal women or those on oestrogen supplements due to the inhibitory effect of oestrogen on growth hormone action.

2.13 The Subcommittee considered that individuals receiving treatment with growth hormone who also required oestrogen supplementation should have access to transdermal patches as individuals on oral oestrogen would require an increased growth hormone dose. Members **recommended** that the Special Authority criteria for transdermal oestrogen be amended to enable individuals who are being treated with growth hormone to access fully funded treatment.

3 Criteria for adolescents with growth hormone deficiency

3.1 The Subcommittee considered that although the majority of adolescents who ceased growth hormone treatment at epiphyseal fusion would not require ongoing therapy and would be happy to stop treatment, approximately 10-15% of adolescents may experience a significant reduction in quality of life and may require ongoing treatment. The Subcommittee noted that there was also a group of growth hormone naïve adolescents who developed GHD after epiphyseal fusion in whom growth hormone therapy may be appropriate.

3.2 The Subcommittee noted that in the United Kingdom the recommendation is to treat all GHD adolescents up to the age of 25 to achieve peak bone mass.

3.3 The Subcommittee noted that PHARMAC had recently approved recommencement of growth hormone in two adolescent patients following a marked decline in quality of life after growth hormone was ceased. The Subcommittee noted that quality of life had been assessed in these individuals using a range of indicators including quality of life questionnaires, body composition, weight, and growth hormone and IGF-1 levels.

3.4 The Subcommittee considered that ideally adolescents with GHD should be assessed under the same criteria as adults with GHD. The Subcommittee noted that the AGHDA questionnaire had not been validated in adolescents and considered that other measures could be used to assess quality of life in this patient population. There was considerable discussion around what the appropriate measures could be. The Subcommittee discussed whether academic performance could be used as a measure of quality of life, but considered that this could discriminate against non-academic adolescents.

3.5 The Subcommittee considered that it would be appropriate for other relevant tests to replace the requirement for an AGHDA score in adolescents. The Subcommittee considered that relevant tests would be a grey area but that the role of the Panel would be to consider applications on a case-by-case basis and determine whether or not treatment was justified. The Subcommittee noted that following the meeting, members would investigate whether there were any questionnaires that had been validated in adolescents with GHD that could be used to determine quality of life. Members considered that adolescents with confirmed severe GHD who have evidence of significantly reduced bone mass for age (Z score < -2) should also be considered for growth hormone replacement therapy on a case by case basis to achieve peak bone mass.

3.6 The Subcommittee discussed the appropriate application process for adolescents with GHD who had met the exit criteria for growth hormone treatment (i.e. those who had ceased growth). The Subcommittee considered that it would be appropriate for patients to remain off treatment for at least three months, after which time they should undergo a thorough reassessment including growth hormone provocation and IGF-1 testing, a

quality of life assessment (or other relevant test), and a supporting statement from the clinician. Applications would then be determined by the Adult Growth Hormone Panel.

3.7 The Subcommittee considered that adolescents should be required to undergo two growth hormone provocation tests, as a number of children are GH sufficient after stopping treatment. In addition to the growth hormone stimulation tests described for adults, arginine is also considered suitable as a growth hormone stimulus in this age group.