

7.10 SOMATROPIN, Multiple forms and strengths, Multiple brands, Endocrine Society of Australia, Australian Paediatric Endocrine Group

1 Purpose of Application

- 1.1 Section 100 (PBS Growth Hormone Program) listing for somatropin for treatment of adults with severe growth hormone deficiency (GHD) and substantially impaired quality of life (QoL) at baseline. This resubmission was based on the submission in July 2011. The first submission was reviewed and rejected in December 2001 (Eli Lilly Australia Pty Ltd). The second resubmission was reviewed and rejected in July 2011 (Pfizer Australia Pty Ltd), on the basis of uncertain clinical benefit and highly uncertain cost-effectiveness (PSD, July 2011, somatropin, p11, paragraph 12).

2 Requested listing

- 2.1 The resubmission requested a Section 100 (PBS Growth Hormone Program) listing.

Name, Restriction, Manner of administration and form	Strength(s)	Pack quantity	DPMQ	Brand name	Sponsors
Somatropin (Recombinant human growth hormone)	Multiple	Multiple	\$44.10 per mg	Multiple	Pfizer Australia Pty Ltd; Eli Lilly Australia Pty Ltd; Novo Nordisk Pharmaceuticals Pty Limited; Ipsen Pty Ltd; and Merck Serono Australia Pty Ltd

Treatment phase	Initial
Treatment criteria	Patient must be treated by an endocrinologist
Clinical criteria	<p>Patient must have childhood onset growth hormone deficiency due to a congenital, genetic or structural cause; OR</p> <p>Patient must have adult onset growth hormone deficiency secondary to organic hypothalamic or pituitary disease</p> <p>AND</p> <p>Patient must have an insulin tolerance test with maximum serum GH<3 µg/l; OR</p> <p>Patient must have an arginine infusion test with maximum serum GH<0.4 µg/l; OR</p> <p>Patient must have an glucagon provocation test with maximum serum GH<3 µg/l</p> <p>AND</p> <p>Patient must have a quality of life score on the QoL-AGHDA instrument for growth hormone deficiency of ≥16</p>
Population criteria	Patient must be aged 18 years or older

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Treatment phase	Continuing
Treatment criteria	Patient must be on somatropin replacement therapy for <12 months, with a dose not exceeding 0.7 mg per day for male patients or 1 mg per day for female patients
Clinical criteria	Patient must maintain IGF-1 levels within the normal range for age and sex, AND Patient must maintain a quality of life score on the QoL-AGHDA instrument for growth hormone deficiency of ≥ 8 points lower than baseline AND Patient adherence must be satisfactory with the patient wishing to continue therapy, as determined by clinician
Population criteria	Patient must be aged 18 years or older
OR	
Treatment length	Patient must be on somatropin replacement therapy for ≥ 12 months, with a dose not exceeding 0.7 mg per day for male patients or 1 mg per day for female patients
Clinical criteria	Patient must maintain IGF-1 levels within the normal range for age and sex, AND Patient must maintain a quality of life score on the QoL-AGHDA instrument for growth hormone deficiency of ≥ 6 points lower than baseline AND Patient adherence must be satisfactory with the patient wishing to continue therapy, as determined by clinician
Population criteria	Patient must be aged 18 years or older

Treatment phase	Recommencement of treatment
Treatment criteria	Patient must be treated by an endocrinologist
Clinical criteria	Patient must have a quality of life score on the QoL-AGHDA instrument for growth hormone deficiency of ≥ 16 AND Patient adherence is satisfactory with the patient wishing to re-commence therapy, as determined by clinician
Population criteria	Patient must be aged 18 years or older

- 2.2 Listing was sought on the basis that somatropin is cost-effective compared with standard care (SC).
- 2.3 The ESC noted that the recommencement criteria required a patient to be adherent to treatment. The ESC considered that this may refer to adherence during the previous course of treatment, noting that adherence could not be demonstrated while a patient is off treatment.
- 2.4 The ESC also noted that it was unclear how a patient who has previously been treated with somatropin, would qualify for treatment as they may not be able to meet the eligibility criteria for substantially impaired QoL at baseline. For instance, the current PBS eligibility criteria for children accessing somatropin do not include QoL measurements. The ESC also noted that no re-assessment period was stipulated, and no definition of what constituted a break in therapy was proposed.
- 2.5 The resubmission proposed initiation criteria, which included that patients must have peak GH concentrations $< 3 \mu\text{g/l}$ following an insulin tolerance test. The ESC noted

that the approved Product Information(s) required patients to have peak GH concentrations <2.5 µg/l following an insulin tolerance test. Extending PBS restriction to include patients with peak GH concentration above the level stipulated in the PI could be construed as PBS subsidy of off-label prescribing.

- 2.6 The proposed criteria included assessment of QoL using the Quality of Life Assessment of Growth Hormone Deficiency in Adults instrument (QoL-AGHDA). The self-administered QoL-AGHDA instrument comprises a set of 25 binary (yes/no) questions such as, “I lack confidence” or, “I have difficulty controlling my emotions”. The items in the QoL-AGDHA are expressed as unsatisfied needs. A score of 1 is given to each item affirmed and these are summed to give the total score. Consequently, a high score on the measure represents poor QoL.
- 2.7 In its Pre-PBAC Response (p2), the applicant noted that the QoL-AGHDA has been recognised by the UK National Institute for Health and Clinical Excellence Committee as the best validated evaluation tool available for the assessment of QoL in adults with GHD. Whilst acknowledging the subjective nature of the QoL-AGHDA, the resubmission stated that the proposed eligibility criteria required patients to have established hypothalamic-pituitary disease and biochemically-confirmed severe GHD, and therefore, it was argued that this minimised the risk of leakage beyond the proposed PBS population.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

3 Background

- 3.1 **TGA status at the time of PBAC consideration:** there are five somatotropin brands currently TGA registered for the treatment of adults with severe GHD.
- 3.2 Somatotropin is currently listed on the PBS for a range of paediatric indications. Somatotropin for the treatment of adults with severe GHD was previously considered by the PBAC in December 2001 and in July 2011. The evaluation of this resubmission was focussed on changes from the most recent resubmission. The ESC noted that the trials presented in the July 2011 resubmission were small, heterogeneous studies with limited follow up. The long-term effectiveness of somatotropin was uncertain.

Table 1: Summary of the previous submission and current resubmission

	Somatropin July 2011	Current resubmission
Requested PBS listing	For adults with severe GHD. Minimum requirement of QoL-AGHDA ≥15. Peak GH concentration <2.5 µg/l following an ITT ≥3 pituitary hormone deficiencies and an IGF-1 level below the age-specific reference range. PBAC Comment: None	Requested listing for initial treatment, continuation treatment and recommencement of treatment. <u>Main changes:</u> Minimum requirement of QoL-AGHDA ≥16; IGF-1 test not required at the initiation of treatment. Peak GH concentrations <3 µg/l following ITT

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	Somatropin July 2011	Current resubmission
Clinical evidence	39 RCTs KIMS database used in economic evaluation PBAC Comment: Patient population in trials not applicable to PBS population (PSD, July 2011, somatropin, p10, paragraph 12)	Holdaway et al. (2015) observational non-comparative study.
Key effectiveness data	QoL-AGHDA: no baseline or improvement values presented; PGWB; Body composition (lean body mass and fat mass) PBAC Comment: QoL-AGHDA baseline was not an eligibility criterion in the trials, this limited applicability (PSD, July 2011, somatropin, p10, paragraph 12).	QoL-AGHDA mean score improvement of 13 points; IGF-1 score improvement to within 1 SD from the mean (appropriate for age and gender).
Key safety data	Presented combined adverse events from the clinical trial reports, a summary of adverse events reported from publications and results from unpublished study. Additional data from PI, open-label period of the clinical trials, PSUR (up to March 2009), two observational studies KIMS and HypoCSS. Most common adverse events from KIMS were arthralgia, influenza-like symptoms, upper respiratory tract infection and headache. PBAC Comment: None.	No data was presented from Holdaway et al. (2015); an update PSURs for the five brands were presented in Section B.8
Clinical claim	Somatropin is superior in terms of comparative clinical effectiveness with respect to QoL, and inferior in terms of comparative safety, compared with placebo. PBAC Comment: Effectiveness: the PBAC concluded that the evidence did not support a claim of superiority for somatropin over placebo in affecting an improvement in QoL. Safety: PBAC accepted this claim in short-term safety, but considered that the long-term safety of somatropin was uncertain (PSD, PBAC July 2011, p.8, paragraph 9).	Somatropin is superior in terms of comparative effectiveness with respect to QoL and non-inferior in terms of comparative safety over standard care.
Economic evaluation	Cost-utility model with cost/QALY \$45,000 - \$75,000. PBAC Comment: the ICER for somatropin compared to placebo treatment was likely to be higher (PSD, PBAC July 2011, p.8, paragraph 9).	Cost-utility model with cost/QALY: \$15,000 - \$45,000 Sensitivity analysis for the change in QoL-AGHDA score from the baseline: \$45,000 - \$75,000.
Number of patients	Less than 10,000 in Year 1 increasing to Less than 10,000 in Year 5. PBAC Comment: None	Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5.

	Somatropin July 2011	Current resubmission
Estimated cost to PBS	Less than \$10 million in Year 1 increasing to less than \$10 million in Year 5 for a total of \$10 - \$20 million over the first 5 years of listing. Excluded patient co-payment. PBAC Comment: None	Less than \$10 million in Year 1 increasing to less than \$10 million in Year 5 for a total of over \$10 - \$20 million the first 5 years of listing. (Values were adjusted to include patient co-payments.)
PBAC decision	Reject on the basis of uncertain clinical benefit and highly uncertain cost effectiveness.	-

Source: Compiled during the evaluation. Abbreviations: PI= Product Information, PSUR= Periodic Safety Update Report, KIMS= Pfizer International Metabolic Database, HypoCSS= Hypopituitary Control and Complications Study, ICER= incremental cost effectiveness ratio, PSD= public summary document, PGWB= Psychological General Well Being, QALY= quality adjusted life years, QoL= quality of life, QoL-AGHDA= quality of life assessment of growth hormone deficiency in adults, GHD= growth hormone disorder, SD= standard deviation.

4 Clinical place for the proposed therapy

- 4.1 Adults with GHD have increased fatigue, lowered endurance, decreased lean muscle mass, increased fat mass and impaired exercise tolerance. Muscle function and cardiac performance assessed by formal measurements are significantly impaired compared with non-GHD subjects. GHD causes a number of adverse metabolic effects including hyperlipidaemia, impaired insulin sensitivity, and abnormal levels of fibrinogen. GH deficient adults also have an increased incidence of osteoporosis and fractures.
- 4.2 GH deficient adults have reduced QoL due to, among other symptoms, mood fluctuations, anxiety, depression, fatigue and lack of strength. The clinical evidence presented in this resubmission only addressed the QoL impairments of GHD.
- 4.3 The resubmission proposed the use of QoL scores assessed using the QoL-AGHDA for treatment initiation, continuation and recommencement. The initiation and recommencement criteria included a baseline measurement (QoL-AGHDA score ≥ 16), and the criteria for continuing treatment varied by treatment duration (score of ≥ 8 points lower than baseline for patient with < 12 months of treatment and ≥ 6 lower than the baseline for patients with ≥ 12 months of treatment). However, the ESC considered that the resubmission did not adequately justify the choice of cut-offs for each of these criteria, the differences between the criterion for continuing treatment based on treatment duration, nor the broader deviations from the PHARMAC criteria for initial and continuing access to somatropin applied within Holdaway et al. (2015).
- 4.4 The Pre-Sub-Committee-Response (PSCR, p2) stated that the choice of cut-off at initiation is “modelled on the reimbursement criteria adopted by the New Zealand PHARMAC for somatropin in the treatment of severe GHD adults with substantially impaired QoL. The QoL cut-off point adopted by PHARMAC (i.e. QoL-AGHDA score ≥ 16 of a maximum of 25) is the most stringent of the major HTA markets. By comparison, the cut-off point for NICE in the UK is a QoL- AGHDA score ≥ 11 .” The Pre-PBAC response (p2) reiterated this view and added that ESA and APEG are open to discuss alternative QoL-AGHDA cut-off points which the PBAC may consider more appropriate.

For more detail on PBAC's view, see section 7 "PBAC outcome".

5 Comparator

- 5.1 The resubmission presented standard care (consisting of regular monitoring by an endocrinologist of appropriate replacement of other hormone deficiencies and management of symptoms and risk factors arising from GHD) as the main comparator. This was the same definition of standard care as in the July 2011 submission, which was previously considered by PBAC to be an appropriate comparator (PSD, PBAC July 2011, Somatropin, p9, paragraph 12).

For more detail on PBAC's view, see section 7 "PBAC outcome".

6 Consideration of the evidence

Sponsor hearing

- 6.1 The applicant requested a hearing for this item. The clinician described the high unmet clinical need of the drug, discussed how the drug is used in practice, and addressed other matters in response to the Committee's questions. The clinician described how patients receiving a benefit from the somatropin are likely to be adherent to therapy and how when therapy is stopped, the clinical features of GH deficiency tend to recur. The evidence in the resubmission (Holdaway et al, 2015) was compared with earlier RCTs, and it was noted that earlier studies had often used generic or non-specific questionnaires and did not always target the cohort of population of patient with the lowest QoL at baseline, as proposed for the PBS population. The Committee asked how a 7-point improvement in QoL would be perceived by a patient, and the applicant remarked that it would mean a marked improvement in their ability to function in society. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating severe GHD in adults.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (68), health care professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with somatropin including the weight loss, improved bone density, muscle and joint strength, mobility, respiratory function, cardiac health and mood. Overall, comments emphasised that somatropin improved energy levels, and quality of life, particularly in relation to work and social functioning. The comments also described the financial burden of taking the treatment over many years.
- 6.3 The PBAC noted the advice received from the Australian Pituitary Foundation and the Endocrine Society of Australia. The President of the ESA, writing an independent clinician, wrote to support the listing of somatropin under this submission. The PBAC noted the advice that the New Zealand experience of somatropin subsidy has been published, that there were methodological shortcomings with earlier trials, and that further large randomised controlled trials were unlikely to be conducted. The PBAC

also noted the advice that patients who do not experience a benefit from somatropin would be unlikely to continue treatment. The PBAC considered that these comments reflected the evidence provided in the submission.

- 6.4 The Australian Pituitary Foundation (APF) wrote to support the submission on behalf of its members. The APF conducted a consumer survey (n=165), and provided patient and carer testimonials. The survey responses described a range of patient demographics, treatment histories and benefits from GH replacement therapy. The patient testimonials included from: adults who had been recipients of GH as a child; parents of children who received therapy who are now adults; adults who acquired GH deficiency later in life who cannot afford therapy; and adults who self-fund and receive benefits from GH therapy. Comments were also received from family and friends supporting the PBS listing of somatropin. The PBAC noted the correspondence from the Pituitary Foundation UK and the International Coalition of Organizations Supporting Endocrine Patients (attached to the APF submission) expressing support for public subsidy of GH replacement therapy.

Clinical trials

- 6.5 The resubmission was based on one non-randomised, single arm observational study of New Zealand patients with severe GHD receiving somatropin under the auspices of the PHARMAC program for subsidised access to somatropin during Holdaway et al. (2015). The July 2011 resubmission was based on 39 randomised controlled trials comparing somatropin with placebo in adult patients with GHD.

- 6.6 Details of the study presented in the resubmission are provided below.

Table 2: Study and associated report presented in the resubmission

Study ID	Protocol title/ Publication title	Publication citation
Included study		
Holdaway	Holdaway, I. M., Hunt, P., Manning, P., Cutfield, W., Gamble, G., Ninow, N., Staples-Moon, D., Moodie, P., & Metcalfe, S. (2015). Three-year experience with access to nationally funded growth hormone (GH) replacement for GH-deficient adults.	July 2015 <i>Clinical endocrinology</i> 2015;83(1): 85-90

Source: Table 16, p21, of the resubmission.

- 6.7 The key features of the Holdaway et al. (2015) study are summarised below.

Table 3: Key features of the included evidence

Study	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Single arm, somatropin						
Holdaway et al. (2015)	201	Observational 33 mths	High	Adults with severe GHD	QoL-AGHDA, IGF-1 score	Basis for QoL changes and treatment utilisation.

Source: compiled during the evaluation. GHD = growth hormone deficiency; QoL-AGHDA = quality of life assessment of growth hormone deficiency in adults; IGF-1 = insulin-like growth factor 1.

- 6.8 The key eligibility criteria in Holdaway et al. (2015) (i.e. the PHARMAC criteria) for accessing somatropin are outlined in the table below.

Table 4: Key eligibility criteria used in the observational study, Holdaway et al. (2015).

Inclusion criteria
<p>All patients</p> <p>Somatropin-naive patients:</p> <ul style="list-style-type: none"> • Age ≥ 18 year old; • GH-deficient as shown in one or more of the following dynamic tests of GH secretion: <ul style="list-style-type: none"> ○ insulin-induced hypoglycaemia with maximum serum GH <3 µg/l; ○ arginine infusion with maximum serum GH <0.4 µg /l; and/or ○ glucagon provocation with maximum serum GH <3 µg/l. • serum IGF-I more than 1 standard deviation (SD) below normal mean for gender and age; • a quality of life score on the QoL-AGHDA instrument ≥ 16; • a medical condition known to cause deficiency; and • other hormone deficiencies and psychological illness should be adequately treated. <p>Patients who had previously self-funded growth hormone treatment (without the appropriate baseline data available) were required to:</p> <ul style="list-style-type: none"> • stop GH treatment for a minimum period of one month; and • undergo full assessment as for somatropin-naïve patients. <p>Individuals who were previously treated with GH under childhood program and who presented for funded treatment as adults were required to:</p> <ul style="list-style-type: none"> • undergo full re-evaluation off the GH treatment for a minimum period of three months. <p>Other requirements:</p> <ul style="list-style-type: none"> • the report from the patient's most recent pituitary MRI scan; • details of any previous treatment with growth hormone, current illness and medications, fasting serum lipids and glucose, HbA1c, serum hormone levels, • waist and body mass index (BMI) measurements; • Epworth Sleepiness Scale (ESS) daytime somnolence score if BMI > 35 (in sleep study if indicated), • bone mineral density; and • statement from referring clinician as to what clinical improvements were expected with GH treatment.
Continuation criteria
<ul style="list-style-type: none"> • Assessment after initial 9 months and then re-approval is considered annually. • Data must include an updated QoL- AGHDA score as well as IGF-I levels, dose of GH, statements on side effects and patient adherence. • Renewal criteria are met for further funding if the IGF-I is within target range, the QoL-AGHDA score has improved by more than 7 points, and patient adherence is satisfactory with the patient wishing to continue therapy. • After the initial dose adjustment period, patients have 6 monthly IGF-I levels to monitor compliance and an annual clinical review including QoL-AGHDA scores and routine biochemistry.
Exit criteria
<ul style="list-style-type: none"> • Patient wishing to stop treatment • Major adverse side effects • Failure to reach/maintain serum IGF-1 within one SD of mean for age/sex despite ceiling doses (0.7mg/day males and 1 mg/day females) • Once stable on treatment, deterioration in AGHDA >5 on two measurements more than 6 months apart (without explanation by coincidental illness or stress) • Unsatisfactory follow-up/compliance

Source: p86, Holdaway et al., 2015.

6.9 With regard to these criteria, the ESC noted:

- The requirement that other hormone deficiencies and psychological illness should be adequately treated was not included in the proposed PBS criteria. The ESC considered that if it were not, there was potential to see larger improvements in

PBS patients with co-existing psychological conditions who may not otherwise qualify for ongoing treatment.

- The study required patients to have peak GH serum as measured by insulin tolerance test, of <3 µg/l. This was included in the proposed PBS criteria, and was not as stringent as in the approved product information (PIs), which stipulate peak GH concentrations <2.5 µg/l following insulin tolerance testing. The use of somatropin for patients with higher peak GH levels than specified in the TGA-registered indication would constitute PBS subsidy of off-label prescribing.
- The timeframe for clinical reassessment in the study was initially 9 months, then every six months (with PHARMAC continuation approval considered annually). No timeframe for reassessment was specified in the proposed PBS criteria. PBS-subsidised treatment usually provides one month's supply per dispensing, with sufficient repeats (if appropriate) for up to six months' supply per prescription.
- "Major adverse side effects" were an exit criterion, yet serious adverse events were not quantified in Holdaway et al. (2015). The ESC considered this important in light of the lack of comparative safety in both this resubmission and the previous submission.
- The study continuation criteria considered response in relation to both baseline measurements, **and** treatment over time. For example, an exit criterion was: deterioration in QoL-AGHDA of more than five points in measurements taken more than six months apart. In contrast, the proposed PBS criteria consider response to treatment in relation only to baseline QoL-AGHDA score. Should the resubmission be recommended by PBAC, the ESC advised that it would be appropriate to include a requirement for response to be measured over time.
- Under the study continuation criteria, patients needed to achieve an improvement in their QOL-AGHDA score >7 points from baseline. The proposed PBS criteria required improvements of ≥8 from baseline at <12 months, or ≥6 from baseline at ≥12 months. No adequate justification for either the deviation or the variation was provided in the resubmission. As proposed, the PBS criteria could allow for patients to have a large response from baseline within the first 12 months, and to then deteriorate by a clinically relevant amount, but to remain on treatment as long as the difference from baseline was ≥6 points.

- 6.10 The ESC noted a 2012 publication of a meta-analysis of 53 RCTs by Hazem et al¹. The ESC noted that this meta-analysis was not included in the resubmission, although the individual RCTs in the meta-analysis were included in the literature search for the July 2011 submission. The ESC advised that the applicant may wish to address the exclusion of this meta-analysis in its pre-PBAC response. In its Pre-PBAC Response (p2), the applicant stated that the meta-analysis was not included because not all of the trials analysed were limited to a severe GHD population and none of the included trials were limited to a population with a substantially impaired QoL. Therefore, the results of the meta-analysis were not applicable to the proposed PBS restriction.

¹ Hazem et al, (2012), "Body composition and quality of life in adults treated with GH therapy: a systematic review and meta-analysis", *Eur J Endocrinol* 166(1):13-20. doi: 10.1530/EJE-11-0558.

Comparative effectiveness

- 6.11 QoL-AGHDA results from Holdaway et al. (2015) are summarised in Table 4 for the treated population.

Table 4: Results of QoL-AGHDA from the observational study

Study ID	Somatropin (mean values, 95%CI)					
	N	Baseline	N	9 months	N	33 months
Holdaway et al. (2015)	191	19 (18, 21)	NR	6 (4, 8)	157	5 (3, 9)

Source: Table 18, p.23 and Table 23, p.28, of the resubmission. Note: CI = confidence interval; QoL-AGHDA = quality of life assessment of growth hormone deficiency in adults; NR = not reported.

- 6.12 The outcomes were assessed only for patients who remained on treatment at 33 months (n=157). The magnitude of the improvement in QoL-AGHDA is likely to be lower if all treated patients were considered. The PBAC previously considered that the patients who continued treatment were the most likely to respond, since patients with adverse events are likely to discontinue.
- 6.13 The PSCR (p2) stated that the exclusion of patients who discontinued treatment in the Holdaway study was justified on the basis of a low rate of treatment discontinuation (17% after 3 years). In addition, the PBS treatment continuation criteria proposed in the resubmission – on the basis of changes in QoL-AGHDA scores – ensures that reimbursement is only provided to individuals benefiting from treatment. Further, in the economic model, the QoL benefits were only applied to individuals remaining on treatment, with those patients discontinuing treatment returning to baseline levels. Therefore, the PSCR claimed that the magnitude of clinical benefit in the cost-effectiveness analysis was not overestimated.
- 6.14 The ESC considered that the magnitude of benefit was likely overestimated. The ESC considered the discontinuation rate not insubstantial given the small sample size (33 discontinuations out of 191 patients recruited). The ESC also noted there was a risk of selection bias as it was not known which potentially eligible GHD patients chose not to enter the PHARMAC-funded somatropin access scheme.
- 6.15 The ESC recalled that in the July 2011 submission, the PBAC noted that the two trials that assessed QoL using the QoL-AGHDA (Chihara 2006 and Mesa 2003) reported no significant effect of treatment with somatropin.
- 6.16 The Pre-PBAC Response (p1-2) agreed that those patients who continue to receive somatropin are those most likely to respond. However, it claimed that due to the “strict continuation criteria proposed in this submission... somatropin will only be reimbursed for those patients experiencing a substantial benefit.” The Pre-PBAC Response argued that since the cost-effectiveness was calculated “inclusive of application of ongoing continuation rules”, it is unlikely that the magnitude of benefit has been over-estimated (“as discontinuing patients have been factored in”).

Comparative harms

- 6.17 The resubmission stated that no serious adverse events (SAEs) were reported in the Holdaway et al. (2015) study. Patients experienced minor side effects when commencing somatropin, including fluid retention, arthralgia and early carpal tunnel symptoms, which were resolved with continuing treatment. However, the study also stated that a more detailed record of the reasons for discontinuation of 33 (17%) participants would have been necessary to understand the occurrence of adverse events. The ESC noted that the exit criteria in the study included “for major adverse side effects”.
- 6.18 The July 2011 resubmission based on 39 RCTs, stated that somatropin appeared to be associated with more adverse events than placebo treatment (PSD, PBAC July 2011, Somatropin, p7, paragraph 8). The weight of evidence therefore suggests that somatropin is associated with more adverse events than placebo.

Benefits/harms

- 6.19 On the basis of a single arm, non-comparative study presented by the resubmission, treatment with somatropin resulted in approximately 14 points improvement from baseline in QoL-AGHDA score for 157 (83%) of patients who remained on treatment at 33 months of follow up.

Clinical claim

- 6.20 The resubmission described somatropin as superior in terms of comparative effectiveness with respect to QoL and non-inferior in terms of comparative safety over standard care.
- 6.21 The ESC noted that the change from baseline in QoL-AGHDA score exceeded the MCID of 4.61 reduction in the mean score at 12 months (Wiid et al., 2013), and that a statistically significant change was achieved and maintained in the serum IGF-I. However, noting the lack of comparative evidence, the ESC did not view the clinical claim as reasonable. The ESC also noted that the claim of superiority in terms of comparative effectiveness would only be reasonable if it is accepted that, in the absence of active therapy, patients with GHD would not experience an improvement in QoL.
- 6.22 The Pre-PBAC Response (p1) argued that poor health due to hormone deficiency, for example hypothyroidism, hypoadrenalism or hypogonadism, does not improve spontaneously. The Response cited a Spanish study in over 350 adult GHD patients, where the reported QoL was significantly impaired compared to a control population and did not change over 12 months (Badia, 1998). In a UK study, QoL declined in untreated GHD patients over 9 years follow-up (Gilchrist et al., 2002). Although not captured in the current submission, the Pre-PBAC Response outlined that the natural history of severe GHD in adults includes decreased bone mineral density, muscle strength, exercise capacity, cognitive function, as well as QoL (De Boer et al., 1995).
- 6.23 In the July 2011 resubmission, based on RCT data, the PBAC concluded that the evidence did not support a claim of superiority for somatropin over placebo in affecting an improvement in QoL.

- 6.24 The safety claim in this submission was not adequately supported. The ESC viewed that that the lack of detailed data regarding the reasons for discontinuing treatment during the 33 months of study follow-up introduces uncertainty into the assessment of safety for somatropin compared to standard care.
- 6.25 The July 2011 submission claimed that somatropin was inferior in terms of short-term safety to placebo. The PBAC accepted this claim but considered that the long-term safety of somatropin was uncertain (PSD, PBAC July 2011, p.8, paragraph 9).
- 6.26 The PBAC considered that the claim of superior comparative effectiveness, in terms of QoL improvement, against standard care was not adequately supported by the data. The clinical benefit was uncertain, and the PBAC, noting the ESC's concerns, agreed it was likely overestimated. The PBAC viewed that a presentation of comparative clinical evidence on the range of physiological effects of somatropin treatment would have provided additional context for interpreting the magnitude of the clinical benefit.
- 6.27 The PBAC considered that the claim of non-inferior comparative safety compared with standard care was not sufficiently supported by presentation of the non-comparative Holdaway et al. 2015 data, especially in view of the lack of details regarding the reasons that patients discontinued treatment during the 33 months study follow-up. The PBAC recalled its previous advice that somatropin was inferior in terms of short-term safety compared to placebo, but noted the possibility that higher treatment doses in earlier studies had influenced this result.

Economic analysis

- 6.28 The economic evaluation is a stepped cost-utility analysis using a Markov model comparing somatropin with standard care (SC).

Table 5: Summary of model structure and rationale

	July 2011	Resubmission
Time horizon	5 year (base case) model based on the data from KIMS dataset.	Lifetime (60 years) (base case; Step 3).
Outcomes	Improvement in QoL-AGHDA points, translated into a utility gain to estimate QALYs.	This is unchanged.
Methods used to generate results	Semi-Markov cohort model based on subgroup of patients from KIMS database.	Markov model based on patients data from Holdaway et al. (2015).
Cycle length	1 month (half cycle correction applied)	This is unchanged.
Discount rate	5% of costs and benefits	This is unchanged.
Software package	TreeAge Pro 2009	TreeAge 2013

Source: compiled during the evaluation. KIMS= Pfizer International Metabolic Database, QALY = quality adjusted life years; QoL = quality of life; QoL-AGHDA = quality of life assessment of growth hormone deficiency in adults.

- 6.29 The economic evaluation included in the July 2011 submission was a stepped cost-utility analysis based on a subgroup analysis of the Pfizer International Metabolic Database (KIMS) observational study in adult GHD patients. A Markov model was presented comparing somatropin with standard care, with a five year time horizon. The model presented in the current resubmission uses the same structure as that presented in July 2011, with the following differences: the current model uses the Holdaway et al. (2015) rather than the KIMS dataset; patients entering the model

have a minimal QoL-AGHDA score of 16 rather than 15; the time horizon in Steps 1 and 2 of the model is 3 years as compared with 1; and the overall model uses a life-time horizon (60 years) as opposed to 5 years.

- 6.30 The PBAC previously noted that:
- KIMS is an observational database which contains few untreated patients, hence PBAC considered the data non-comparative and likely to be highly selective of patients successfully treated with somatropin;
 - The clinical reasons for selecting the baseline QoL-AGHDA score were unclear;
 - The patients who did not have follow-up at each point were excluded from the analysis, with 390 patients with a QoL-AGHDA of 15 or greater at baseline reducing to 17 patients at year 5; the PBAC considered this exclusion a source of bias in favour of somatropin in that the patients who continued were the most likely to be responding to treatment as those with lack of efficacy and adverse effects were more likely to discontinue treatment (PSD, July 2011, somatropin, p.10-11, paragraph 12).
- 6.31 The use of the Holdaway et al. (2015) data in the economic evaluation in this resubmission did not advance these issues given that it is also an observational database which contains no untreated patients, and a convincing clinical rationale for the choice of a baseline score of 16 as defining GHD warranting treatment was not provided.
- 6.32 The ESC noted that 17% of patients withdrew from the study. Holdaway et al. (2015) stated that “in a minority of patients”, this was due to “treatment failing to achieve appropriate improvement in QoL-AGHDA or IGF-I SD score” (p88). The ESC considered that a treatment effect based on 83% of participants overestimated the expected effect on QoL-AGHDA. At the same time, the model assumed that patients discontinuing GH therapy return to baseline QoL-AGHDA score, which could potentially be an underestimate.
- 6.33 The QoL-AGHDA instrument comprises 25 binary questions. The Holdaway data (reflecting PHARMAC criteria), included a requirement of QoL-AGHDA ≥ 16 for commencing treatment; QoL-AGHDA improvement ≥ 7 for continuing treatment. The ESC considered that there was a risk that patients may have provided responses to the QoL-AGHDA questions that would enable access to subsidised treatment. Consequently, there was a risk that the observed treatment effect was overstated.
- 6.34 The model assumed a constant treatment effect after 18 months of treatment, based on data from 33-months of non-comparative study; this favoured somatropin. The PSCR (p3) stated that there is no evidence in the published literature regarding a waning in the treatment effect for somatropin; rather, the evidence demonstrates that improvements in QoL are sustained while patients are on GH replacement therapy. The PSCR (p3) argued that this was a conservative assumption. It suggested that patients who remained on treatment in Holdaway et al. (2015) actually had a larger improvement in QoL over 33 months (an average of 5 points on the QoL-AGHDA score), than was modelled – that is, the average QoL-AGHDA score did not drop below 6 points after 18-months of treatment. The ESC considered this claim did not account for the impact of patients leaving the study after 18 months, and concluded that the possibility of waning treatment effect had not been excluded by the resubmission.

- 6.35 The Pre-PBAC Response (p3) reiterated its claim that the effects of hormone replacement do not wane. It argued that the clinical evidence demonstrates that improvements in QoL are sustained while patients are on GH replacement therapy (Appelman-Dijkstra et al., 2013, Gilchrist et al., 2002, Kołtowska-Hägström et al., 2006).
- 6.36 In the absence of GH treatment, the model assumed constant QoL-AGHDA scores ≥ 16 . This did not appear to reflect patient experience in the RCT data presented in the previous resubmission. The Pre-PBAC Response (p2-3) argued that RCT evidence previously presented is not applicable to the proposed PBS population in the current submission. It was stated that the RCT data likely included patients with mild GHD or possibly without GHD because of the use of non-validated diagnostic tests.
- 6.37 The representativeness of the Holdaway et al. (2015) study for the PBS population was unclear, due to a higher proportion of female patients in the study at baseline who also have a higher mean dose of somatropin; and the varied ethnic background of the participants in the study, which would differ from the Australian population; the resubmission did not provide an assessment of the extent of these differences.
- 6.38 The resubmission used EQ-5D based utility scores in the economic model, produced by mapping from the QoL-AGHDA values using the same mapping formula as in the July 2011 resubmission. The mapping formula is based on mapping from QoL-AGHDA to EQ-5D of a large Swedish general population sample and assumed 100% correlation between these instruments. The PBAC has previously considered this increased the uncertainty of the mapping results (PSD, PBAC July 2011, p. 11, paragraph 12).
- 6.39 The aggregate mapping formula applied a constant utility decrement of 0.0189 for each of the 25 binary items in the QoL-AGHDA instrument. A more recent mapping paper showed large variation in utility effects across the 25 items (Busschbach et al., 2011). Individual coefficients for each binary item were reported, which included:
- In the Belgian cohort: 5 items with positive utility effects, and 5 items with a utility decrement greater than 0.03 and maximum utility decrement of 0.094.
 - In the Dutch cohort: 6 items with positive utility effects, and 7 items with a utility decrement greater than 0.03 and maximum utility decrement of 0.17.
- The ESC considered that this more recent mapping paper showed that particular items were driving EQ-5D values. Across the two cohorts, the items with the largest coefficients when mapping to the EQ-5D were: “it takes a lot of effort for me to do simple tasks”, “I feel as if I’m a burden to people”, “I feel worn out even when I’ve not done anything” and “I often feel very tense”. The ESC therefore considered that the assumption of a constant utility decrement across the 25 binary items in QoL-AGDHA instrument was inappropriate.
- 6.40 The transformation was applied on a cohort basis using mean QoL-AGHDA values and proportions for gender, rather than on an individual patient basis as intended by the developers of the mapping function.
- 6.41 The key model drivers are summarised in Table 6.

Table 6: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	60 years; assumed estimated effect is maintained from 33 months trial duration.	Moderate, favours somatropin.
Assumed QoL-AGHDA points improvement	13 points, based on single arm study with measurement issues and 17% dropout rate.	High, favours somatropin.
Proportion of gender in the cohort	58% female from the Holdaway et al. (2015) study.	Low, favours SC.
Utility coefficient	Applied a constant utility decrement per QoL-AGHDA item. The ESC noted that this ignored evidence of variation and that utility effects were driven by a small number of items.	Unclear, but likely to be moderate to high and to favour somatropin.

Source: compiled during the evaluation. QoL-AGHDA = quality of life assessment of growth hormone deficiency in adults, SC = standard care; SEM = standard error of the mean, QoL-AGHDA = quality of life assessment of growth hormone deficiency in adults.

- 6.42 The resubmission assumed that each patient remaining on treatment after 18 months experienced a fall in QoL-AGHDA score to a mean of 6 points from baseline (19 points). The basis of this assumption was not presented in the resubmission. The ESC considered this assumption was inadequately supported, noting that the two trials that assessed QoL using the QoL-AGHDA (Chihara 2006 and Mesa 2003) in the July 2011 submission reported no significant effect of treatment with somatropin.
- 6.43 The resubmission excluded the costs of thyroid function and glucose tolerance tests for monitoring dose and efficacy. It also did not include costs and effects associated with somatropin-related adverse events. These costs and effects would result from treatment with somatropin, thus their exclusion impacts the estimated ICER, possibly in favour of somatropin.
- 6.44 The Pre-PBAC Response (p3) argued that the costs and QoL effects associated with somatropin adverse events were negligible and therefore not incorporated in the economic model. It considered that the QoL-AGHDA captured significant adverse events in patients; if patients have significant adverse events, they would discontinue treatment with somatropin.
- 6.45 The requested PBS criteria include re-treatment, but the costs and benefits associated with re-treatment were excluded from the economic model and financial estimates in the resubmission.
- 6.46 Additionally, the resubmission did not provide an explanation for the selection of the fees for medical costs. However, the ESC noted that the choice of MBS Item numbers with higher fees did not have a large impact on the ICER.
- 6.47 The results of the stepped economic evaluation for the resubmission are presented in Table 7.

Table 7: Results of the stepped economic evaluation

Step and component	Somatropin	Standard care	Increment
Step 1: Holdaway et al. (2015) study-based (3 years) costs and outcomes (undiscounted)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
Outcome: QoL-AGHDA score improvement	13 points	0 points	13 points improvement in QoL-AGHDA
ICER per 1 point of improvement in QoL-AGHDA gained			\$ [REDACTED]
Step 2: Holdaway et al. (2015) study-based (3 years) costs and outcomes (QALYed)			
Costs	\$ [REDACTED]	\$438	\$ [REDACTED]
QALY gained	2.03	1.57	0.46
Incremental cost/ QALY gained			\$ [REDACTED]
Step 3: Lifetime model, discounted (base case)			
Costs	\$ [REDACTED]	\$2,573	\$ [REDACTED]
QALY gained	10.75	8.80	1.95
Incremental cost/ QALY gained			\$ [REDACTED]

Source: Table 44, p.68, of the resubmission. Abbreviations: QoL-AGHDA = quality of life assessment of growth hormone deficiency in adults, QALY = quality adjusted life years.

- 6.48 The estimated ICER presented in the July 2011 submission was \$45,000 - \$75,000 per QALY based on a five year model duration. A sensitivity analysis was conducted in the resubmission using a five year time horizon, resulting in an estimated ICER of \$15,000 - \$45,000. The resubmission presented univariate and multivariate sensitivity analyses. The changes in parameters resulted in a moderate impact on the ICER.
- 6.49 The ICER is most sensitive to the assumption of a 13-point improvement in QoL-AGHDA scores in somatropin treated patients. Reducing the change in severity score to that in the proposed PBS restriction (≥ 8 points within the first year of treatment, ≥ 6 points thereafter) more than doubled the ICER from \$15,000 - \$45,000 per QALY gained to \$45,000 - \$75,000 per QALY gained.
- 6.50 The Pre-PBAC Response (p2) argued that the reported base case ICER of \$15,000 - \$45,000 per QALY is appropriately based on the average 13-point improvement in the QoL-AGHDA score reported by Holdaway et al. (2015) for a patient group with the same eligibility criteria used in this submission. The applicant asserted that it is inappropriate to base the economic modelling on the minimum change in severity score as proposed in the PBS restriction. It acknowledged that the ICER for patients who met the minimum initiation and continuation criteria is \$45,000 - \$75,000, tested in sensitivity analysis. However, there were also patients who received a greater than 13 point improvement in QoL-AGHDA score and the ICER for these patients was substantially less than \$15,000 - \$45,000.
- 6.51 Overall, the cost-effectiveness of somatropin remains uncertain due to the non-comparative nature of the source data, the transformation applied to estimate utility values, the exclusion of the costs and benefits associated with re-treatment, and the exclusion of costs and QoL effects associated with somatropin-related adverse effects.

Drug cost/patient/year: \$7,243.43 for females and \$4,989.92 for males.

6.52 The dispensed cost per milligram for somatropin is \$44.10. The mean dose for females is 0.45 mg/day, and for males is 0.31 mg/day. The annual treatment cost for females is $[(0.45\text{mg} \times 365) \times \$44.10]$, and for males is $[(0.31\text{mg} \times 365) \times \$44.10]$. Treatment is administered daily, on an ongoing basis. For patients who discontinue treatment, a six month treatment duration was assumed. Based on the discontinuation rate from Holdaway et al. (2015), 50% of patients will have discontinued somatropin at 10 years. However, the requested PBS criteria include re-treatment, which was excluded from the economic model and financial estimates in the resubmission.

Estimated PBS usage & financial implications

6.53 This resubmission was considered by DUSC. The resubmission used an epidemiological approach to estimate the net financial impact of including somatropin on the PBS. The cost to the PBS was calculated based on the estimated proportion of adults with severe GHD (25% with QoL-AGHDA ≥ 16 , versus 33% for QoL-AGHDA ≥ 15 from July 2011 submission), the assumed uptake of somatropin (35% in Year 1 reaching 90% in year 5) and a discontinuation rate of 6.02% per year (Holdaway et al. (2015)).

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number of treated patients	█	█	█	█	█
Number of treated patients from July 2011	█	█	█	█	█
Uptake rate	█%	█%	█%	█%	█%
Uptake rate July 2011	█%	█%	█%	█%	█%
Total number of prescriptions/packs per year ^a	█	█	█	█	█
Total number of prescriptions/packs per year from July 2011 submission	█	█	█	█	█
Estimated net cost to PBS/MBS					
Net cost to PBS (including co-payment)	\$█	\$█	\$█	\$█	\$█
Net cost to PBS July 2011 (excluding co-payment)	\$█	\$█	\$█	\$█	\$█
Net cost to MBS	\$█	\$█	\$█	\$█	\$█
Net cost to MBS from July 2011	\$█	\$█	\$█	\$█	\$█
Estimated total net cost					
Net cost PBS/MBS (including co-payment)	\$█	\$█	\$█	\$█	\$█
Net cost PBS/MBS July 2011 (excluding co-payment)	\$█	\$█	\$█	\$█	\$█

Source: Compiled during the evaluation. Tables E.2, E.3 E.5.1 of the commentary. Note: a = 20 estimated average number of packs per patient per year, based on mean dose for males and females and a 50/50 utilization of 5mg and 12 mg packs. Abbreviations: PBS = pharmaceutical benefits scheme, MBS = Medicare benefits scheme.

6.54 The resubmission estimated that the net cost to the government will be less than \$10 million in the first year and less than \$10 million in the fifth year and \$10 - \$20 million

over the first five years of being listed. The resubmission assumed that patients who access somatropin on the PBS would not be charged a co-payment. As of September 2015 this is no longer the case. The net cost to the PBS will thus be reduced by the payment of patient co-payments on a per-supply basis. Including co-payment, the estimated net cost to the government health budget associated with listing somatropin on the PBS for the treatment of severe GHD adult patients with substantially impaired quality of life is less than \$10 million in the first year, increasing to less than \$10 million in the fifth year, with a total of \$10 - \$20 million over five years.

- 6.55 However, there is a potential for the number of prescriptions to be greater than estimated due to more patients meeting the proposed criteria for severe GHD. If the proportion of patients with QoL-AGHDA ≥ 16 is 35%, as presented in the sensitivity analysis, then the net cost to the government will be less than \$10 million in the first year, less than \$10 million in the fifth year, and a total of \$10 - \$20 million over five years.
- 6.56 Overall, the DUSC considered that the estimates presented in the resubmission were likely to be underestimated. The DUSC viewed that the main issues were:
- The number of eligible patients with severe GHD and a QoL-AGHDA score ≥ 16 is likely to be underestimated as the QoL instrument is self-assessed and subjective. There is potential for more patients to meet the severity criteria.
 - The estimated number of eligible patients was uncertain as it was based on the opinion of one clinician.
 - It was inappropriate to convert the discontinuations after three years from the Holdaway et al (2015) study into an annual discontinuation rate, as most patients were treated for less than three years. The proportion of patients discontinuing treatment was underestimated.
 - The submission's approach to the financial estimates was inconsistent and unclear. The submission inappropriately combined both prevalence and incidence approaches resulting in a number of uncertainties.
- 6.57 The number of patients eligible for somatropin on the PBS was estimated by assuming that 25% of adult GHD patients have a QoL-AGHDA score ≥ 16 . This was uncertain as it was based on personal communication with one clinician. The PSCR (p3) stated that due to the lower than globally-accepted insulin tolerance test threshold for GHD diagnosis that has been applied in the resubmission, 25% is an overestimate. The DUSC noted that meeting the insulin tolerance test threshold is not necessary to qualify for the requested restriction, as patients may instead qualify based on results of an arginine infusion test or a glucagon provocation test, thus the applicant's comment is not broadly applicable to the total eligible population. A sensitivity analysis (PSCR, p4) showed that if the proportion of patients with QoL-AGHDA ≥ 16 is increased to 35%, then the net cost to the government would be a total of \$20 - \$30 million over five years compared to \$10 - \$20 million when a 25% rate was used (includes calculation of co-payments). The DUSC reiterated that the QoL-AGHDA instrument is based on a questionnaire that is self-reported and is highly subjective and that the number of eligible patients may be underestimated.
- 6.58 As noted above, the DUSC viewed that the estimated number of eligible patients was uncertain as it was based on the opinion of one clinician. The Pre-PBAC Response (p3) argued that this opinion "is evidence-based using data from prevalence studies."

The UK prevalence rate of 0.02% (Bryant et al., 2002) was chosen for the base-case, as it was considered the most applicable source for the Australian population. A range of prevalence estimates were tested in a sensitivity analysis; 0.015% at the lower range and 0.023% at the upper range as this was the most recent data (Fernandez-Rodriguez et al., 2013). The proportion of patients meeting the restriction criteria proposed in this resubmission is estimated to be 25% of all patients with GHD. This 25% estimate is consistent with the New Zealand experience (Holdaway et al. 2015), where the number of eligible patients with severe GHD and substantially impaired QoL accessing funded treatment in the initial 3 years of their program was 191, from an expected 400-600 patients with GHD (of varying severity) given the NZ population of approximately 4.4 million (estimated from Schneider et al., 2007).

Financial Management – Risk Sharing Arrangements

- 6.59 The resubmission did not propose any Risk Sharing Arrangement, although the PBAC noted that such proposals would likely be beyond the scope of a submission not lodged by a sponsor.

For more detail on PBAC's view, see section 7 "PBAC outcome".

7 PBAC Outcome

- 7.1 The PBAC decided to defer making its decision on whether to list somatropin on the PBS for the treatment of adults with severe growth hormone deficiency (GHD) and substantially impaired quality of life (QoL) at baseline. In making this decision, the PBAC viewed that although there was a place for this drug in therapy for adults with severe GHD, the clinical benefit in terms of QoL was uncertain and the magnitude was likely overestimated, and consequently the PBAC was uncertain as to the cost-effectiveness of the drug for this indication. The PBAC deferred its decision to seek further comparative analysis on the range of clinical benefits provided by somatropin, to clarify the proposed PBS restriction, and to allow the Department to discuss appropriate pricing in this setting with sponsors of somatropin products registered for use in adults.
- 7.2 The PBAC considered that the consumer comments received in relation to the resubmission, both from people living with the GH deficiency and on behalf of patients, were informative in providing a clinical perspective on this condition, particularly in terms of quality of life improvements.
- 7.3 In terms of the place in clinical therapy, the PBAC acknowledged that there was a place for somatropin in the treatment of adults with severe GHD. However, the PBAC noted that the resubmission only presented evidence addressing the QoL impairments of GHD – for which the benefit of somatropin treatment remained uncertain – and not the range of physiological impacts including adverse metabolic effects and reduced bone density. The PBAC viewed that somatropin had a role to play in treating these aspects of the disease, and that the presentation of relevant comparative clinical evidence would have provided a stronger basis for PBAC's assessment of the clinical need and benefit of this therapy.
- 7.4 In its consideration of the requested PBS restriction, the PBAC agreed with the

ESC's concerns (paragraphs 2.3-2.5 and 6.9), and considered that the applicant would need to refine the requested listing to address these issues – in particular adequate justification of the choice of QoL-AGHDA score cut-off values for initiation, continuation and recommencement. Additionally to the ESC advice, the PBAC also noted that the initiation criteria did not require IGF-1 to be documented at initiation of treatment and considered that this would be useful to ascertain GH deficiency, and provide a baseline for ongoing assessment.

- 7.5 The PBAC noted that the resubmission nominated standard care as the comparator, and considered this to be appropriate.
- 7.6 The PBAC noted that the key clinical evidence presented was one non-randomised, single arm observational study of New Zealand patients with severe GHD receiving somatropin under the auspices of the PHARMAC program for subsidised access to somatropin during Holdaway et al. (2015). The PBAC considered that the lack of comparative evidence on the range of physiological effects of treatment limited the interpretability of the claimed clinical benefit.
- 7.7 In the absence of comparative data, the PBAC considered that the comparative effectiveness over standard care, in terms of QoL improvement, was difficult to quantify. The PBAC noted the arguments raised by the PSCR, the ESC advice and the Pre-PBAC Response (paragraphs 6.13-6.16), and agreed with the ESC that the claimed clinical benefit was likely overestimated. The PBAC considered that a presentation of comparative clinical evidence on the range of physiological effects of somatropin treatment would have provided additional context for interpreting the magnitude of the clinical benefit.
- 7.8 The PBAC considered that the claim of non-inferior comparative safety over standard care was not sufficiently supported by presentation of the non-comparative Holdaway et al. 2015 data, especially in view of the lack of details regarding the reasons that patients discontinued treatment during the 33 months study follow-up. The PBAC recalled its previous advice that somatropin was inferior in terms of short-term safety compared to placebo, but acknowledged the possibility that higher treatment doses in earlier studies had influenced this result.
- 7.9 In its consideration of the economic analysis presented in the submission, the PBAC noted several issues with the model inputs, which introduced uncertainty to the ICER calculations. The main concern was the use of Holdaway et al. (2015) data, which contained no untreated patients and was thus likely to be highly selective of patients successfully treated with somatropin. The PBAC shared the concerns raised during the evaluation (see 6.31-6.50), and considered that, given the high uncertainty in quantifying the clinical benefit of somatropin treatment, a reduction in drug cost would improve the cost-effectiveness of somatropin in this setting.
- 7.10 The PBAC considered that the utilisation and financial impact estimates were likely underestimated, noting the subjective self-assessment inherent in the QoL-AGHDA. The PBAC also noted that the assumed number of eligible patients (25%) was based on personal communication with one clinician. The PBAC agreed with the DUSC that the approach to the financial estimates was inconsistent and unclear, resulting in a number of uncertainties. The PBAC considered that addressing the aforementioned

issues with the PBS restriction criteria may reduce some of the uncertainty of these estimates.

- 7.11 In deferring making its decision on whether to list somatropin on the PBS for treatment of adults with GHD, the PBAC considered that in order to quantify the clinical benefit and introduce additional certainty to the assessment of cost-effectiveness in this setting, it required the applicant to provide further comparative analysis on the range of clinical benefits provided by somatropin and apply refinements to the proposed PBS restriction.
- 7.12 The Committee requested that the Department discuss the cost of somatropin in this setting with affected sponsors.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The ESA and APEG will continue to work with the PBAC and the Department to ensure somatropin is available to adults with severe growth hormone deficiency.