

4.05 SOMATROPIN

**multiple forms and strengths, multiple brands,
Endocrine Society of Australia and Australian Paediatric
Endocrine Group**

1 Purpose of Application

- 1.1 The minor resubmission requested a Section 100 (Growth Hormone) Authority Required listing for the treatment of adults with severe growth hormone deficiency (GHD) and substantially impaired quality of life (QoL) at baseline.

2 Background

- 2.1 TGA status: there are five sponsors with forms of somatropin listed on the PBS which are currently TGA registered for the treatment of adults with severe GHD.
- 2.2 Somatropin is currently listed on the PBS for a range of paediatric indications. Somatropin for the treatment of adults with severe GHD was previously considered by the PBAC in December 2001 (rejected), July 2011 (rejected) and November 2016 (deferred). A comparison of the July 2011 submission, November 2016 resubmission and the current resubmission is presented in the table below.

Table 1: Comparison of submissions for somatropin for adults with GHD

| Component | July 2011 | November 2016 resubmission | Current resubmission |
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| Requested PBS listing | <p>For adults with severe GHD. Minimum requirement of QoL-AGHDA ≥ 15. Peak GH concentration $< 2.5 \mu\text{g/l}$ following an ITT ≥ 3 pituitary hormone deficiencies and an IGF-1 level below the age-specific reference range. PBAC Comment: None</p> | <p>Requested listing for initial treatment, continuation treatment ($<$ and ≥ 12 months) and recommencement of treatment for adults with severe GHD. <u>Main changes:</u> Minimum requirement of QoL-AGHDA ≥ 16; IGF-1 test not required at the initiation of treatment. Peak GH concentrations $< 3 \mu\text{g/l}$ following ITT PBAC Comment: Numerous issues, including:</p> <ul style="list-style-type: none"> • Choice of QoL-AGHDA score cut-off values for initiation, continuation and recommencement were inadequately justified. • IGF-1 test not required at the initiation of treatment (needed for baseline values). • Re-commencement criteria unclear. • Peak GH concentrations $< 3 \mu\text{g/l}$ following ITT, inconsistent with TGA PI ($< 2.5 \mu\text{g/l}$ following ITT). • No timeframes for reassessment for continuation of therapy. • No requirement for response to be measured over time (not just from baseline). <p>(Paragraphs 2.3-2.5, 6.9 and 7.4)</p> | <p>Requested listing for initial treatment, continuation treatment (every 12 months) and recommencement of treatment for adults with severe GHD. <u>Main changes:</u></p> <ul style="list-style-type: none"> • IGF-1 test required at initiation to establish a baseline for dosage monitoring. • Peak GH concentrations $< 2.5 \mu\text{g/l}$ following ITT, consistent with TGA PI. • Timeframe for clinical reassessment = every 12 months. • Additional criterion that “patient must not have experienced major treatment-related adverse side effects”. • Adherence requirement for recommencement of therapy refers to adherence during previous course of therapy. |
| Clinical evidence | <p>39 RCTs KIMS database used in economic evaluation PBAC Comment: Patient population in trials not applicable to PBS population (p10, paragraph 12)</p> | <p>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). PBAC Comment: The lack of comparative evidence on the range of physiological effects of treatment limited the interpretability of the claimed clinical benefit. (Paragraph 7.6).</p> | <p>No new clinical evidence presented. Discussion of the effects of somatropin on:</p> <ul style="list-style-type: none"> • Body composition and bone mineral density, • Cardiovascular risk, • Cardiorespiratory function. <p>Discussion on safety. Discussion on various QoL assessment instruments, including the QoL-AGHDA. Re-presents data primarily from qualitative review by Lipworth <i>et al</i>, (March 2014): “Report summarising outcomes of preliminary ESA/APEG working group analysis”.</p> |
| Key effectiveness data | <p>QoL-AGHDA: no baseline or improvement values presented; PGWB; Body composition (lean body mass and fat</p> | <p>QoL-AGHDA mean score improvement of 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. IGF-1 score improvement to within 1 SD from the mean (appropriate for age and</p> | <p>Key data unchanged. The minor resubmission presented a narrative review on the effects of somatropin on body composition and bone mineral density, cardiovascular risk, and cardiorespiratory function.</p> |

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| Component | July 2011 | November 2016 resubmission | Current resubmission |
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| | <p>mass) PBAC Comment: QoL-AGHDA baseline was not an eligibility criterion in the trials, this limited applicability (p10, paragraph 12).</p> | <p>gender). PBAC Comment: ...comparative effectiveness over standard care, in terms of QoL improvement, was difficult to quantify. ...the 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. (Paragraph 7.7).</p> | |
| Key safety data | <p>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.</p> | <p>Updated PSURs for the five brands were presented in Section B.8. The resubmission stated that no serious adverse events (SAEs) were reported in the Holdaway et al. (2015) study. No data was presented in Holdaway et al. (2015). PBAC Comment: The PBAC noted the lack of details regarding the reasons that patients discontinued treatment (17%) during the 33 months study follow-up. (Paragraph 7.8).</p> | Unchanged. |
| Clinical claim | <p>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</p> | <p>Somatropin is superior in terms of comparative effectiveness with respect to QoL and non-inferior in terms of comparative safety over standard care. PBAC Comment: Claims were not sufficiently supported by the non-comparative data presented. Clinical benefit was likely overestimated, and the presentation of comparative clinical evidence on the range of physiological effects of somatropin treatment would have provided additional context. (Paragraph 6.26) 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. (Paragraph 7.8).</p> | <p>Somatropin is superior in terms of comparative effectiveness over standard care, with respect to QoL, body composition, cardiorespiratory function, and metabolic status and non-inferior in terms of comparative safety over standard care.</p> |

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| Component | July 2011 | November 2016 resubmission | Current resubmission |
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| | of somatropin was uncertain (p.8, paragraph 9). | | |
| Economic evaluation | <p>Cost-utility model \$45,000/QALY – \$75,000/QALY</p> <p>PBAC Comment: the ICER for somatropin compared to placebo treatment was likely to be higher (July 2011 Public Summary Document (PSD), p.9).</p> | <p>Cost-utility model \$15,000/QALY - \$45,000/QALY</p> <p>Sensitivity analysis for the change in QoL-AGHDA score from the baseline: \$█.</p> <p>PBAC Comment: Several issues introduced uncertainty to the ICER calculations, including that Holdaway et al. (2015) data contained no untreated patients and was thus likely to be highly selective of patients treated with somatropin. Given the high uncertainty in quantifying the clinical benefit of somatropin treatment, a reduction in drug cost would improve the cost-effectiveness in this setting. (Paragraph 7.9).</p> | Unchanged. ESA/APEG noted that they do not set the price of somatropin. |
| Number of patients | <p>Less than 10,000 per year in Year 1 increasing to less than 10,000 per year in Year 5 (Nov 2016 PSD, paragraph 6.53)</p> <p>PBAC Comment: None</p> | <p>Less than 10,000 per year in Year 1 increasing to Less than 10,000 per year in Year 5. Considered by the DUSC. (Paragraph 6.53)</p> <p>PBAC Comment: Likely underestimated, noting the subjective self-assessment in the QoL-AGHDA. The assumed number of eligible patients (25%) was based on personal communication with one clinician. (Paragraph 7.10).</p> | Unchanged. |
| Estimated cost to PBS | <p>Less than \$10 million in Year 1 increasing to less than \$10 million per year in Year 5 for a total of \$10 – \$20 million over the first 5 years of listing. No patient co-payments were charged under the Growth Hormone Programme prior to 1 September 2015. (Nov 2016 PSD, paragraph 6.53)</p> <p>PBAC Comment: None</p> | <p>Less than \$10 million in Year 1 increasing to less than \$10 million in Year 5 for a total of \$10 – \$20 million in the first 5 years of listing. (Nov 2016 PSD, paragraph 6.53)</p> <p>(Values were adjusted during evaluation to remove patient co-payments, introduced on 1 September 2015.)</p> <p>PBAC Comment: Inconsistent and unclear approach, resulting in uncertainties. Addressing some of the issues with the PBS restriction may reduce some uncertainty. (Paragraph 7.10).</p> | Unchanged. |
| PBAC decision | Reject on the basis of uncertain clinical benefit and highly uncertain cost effectiveness. | Deferred, 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. | - |

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Source: Compiled during the November 2016 evaluation. Amended by the PBAC Secretariat, May 2017. Paragraph references for July 2011 refer to the somatropin public summary document, unless specified otherwise. Paragraph references for November 2016 refer to the somatropin minutes.

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, TGA PI = Therapeutic Goods Administration approved Product Information.

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

3 Requested listing

3.1 The resubmission requested the following new listing. Changes from the listing requested in the November 2016 resubmission are emphasised in italics in the tables below.

Table 2: Proposed PBS restriction for somatropin (initial treatment) for 12 months

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|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Treatment criteria | Patient must be treated by an endocrinologist |
| Treatment length | <i>The maximum duration of the initial treatment phase is 12 months.</i> |
| Clinical criteria | <p>Patient must have childhood onset growth hormone deficiency due to a congenital, genetic or structural cause; OR Patient must have adult onset growth hormone deficiency secondary to organic hypothalamic or pituitary disease <i>Patient must have IGF-1 measurement to establish a baseline for dosage monitoring</i> AND Patient must have an insulin tolerance test with maximum serum GH $\leq 3 < 2.5 \mu\text{g/l}$; OR Patient must have an arginine infusion test with maximum serum GH $< 0.4 \mu\text{g/l}$; OR Patient must have a glucagon provocation test with maximum serum GH $< 3 \mu\text{g/l}$ AND 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 |

Table 3: Proposed PBS restriction for somatropin (continuing treatment) – every 12 months

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|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Treatment criteria | Patient must be on somatropin replacement therapy with a dose not exceeding 0.7mg per day for male patients or 1mg per day for female patients |
| Treatment length | <i>The maximum duration of each continuing treatment authority is 12 months</i> Patient must be on somatropin replacement therapy for ≥ 12 months |
| 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 or $\geq 6 > 7$ points lower than baseline AND Patient adherence must be satisfactory with the patient wishing to continue replacement therapy, as determined by clinician <i>Patient must not have experienced major treatment-related adverse side effects</i> |
| Population criteria | Patient must be aged 18 years or older |

Table 4: Proposed PBS restriction for somatropin (recommence of treatment)

| | |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Treatment criteria | Patient must be treated by an endocrinologist |
| Treatment length | <i>The maximum duration of the recommencement treatment phase is 12 months</i> |
| Clinical criteria | Patient must have a quality of life score on the QoL-AGHDA instrument for growth hormone deficiency of ≥ 16 AND Patient adherence <i>during previous course of treatment</i> is satisfactory with the patient wishing to re-commence replacement therapy, as determined by clinician Patient must not have experienced major <i>treatment-related</i> adverse side effects |
| Population criteria | Patient must be aged 18 years or older |

3.2 The PBAC previously deferred its recommendation in order to clarify the PBS restriction, among other matters. A summary of these concerns and how the minor resubmission addressed them is presented in the table below.

Table 5: PBAC matters of concern with the PBS restriction in previous resubmission, November 2016

| Matters of concern with the PBS restriction (paragraphs 2.3-2.5, 6.9 and 7.4) | How the resubmission addressed it Restriction revised (pp3-6). |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| "...adequate justification of the choice of QoL-AGHDA score cut-off values for initiation, continuation and recommencement." Under the study continuation criteria, patients needed to achieve an improvement in their QOL-AGHDA score > 7 points from baseline. However, the proposed PBS criteria for improvements in QoL-AGHDA score (≥ 8 lower than baseline at < 12 months, or ≥ 6 lower than baseline at ≥ 12 months.) No adequate justification for either the deviation or the variation was provided. (Paragraphs 6.9 and 7.4) | Continuation criterion amended to require patients to maintain a QoL score > 7 points lower than baseline. No additional justifications for cut-off scores provided. |
| Initiation requirement for peak GH concentrations $< 3 \mu\text{g/l}$ following ITT, inconsistent with TGA PIs ($< 2.5 \mu\text{g/l}$ following ITT). (Paragraphs 2.5, 6.9 and 7.4) | Initiation requirement amended in line with TGA PIs. |
| "...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." (Paragraph 7.4) | Clinical criterion added to initiation restriction: "Patient must have an IGF-1 measurement to establish a baseline for dosage monitoring". |

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| Matters of concern with the PBS restriction (paragraphs 2.3-2.5, 6.9 and 7.4) | How the resubmission addressed it Restriction revised (pp3-6). |
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| “...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.” (Paragraphs 2.3 and 7.4) | Recommencement criterion amended: “Patient adherence <i>during previous course of treatment</i> is satisfactory with the patient wishing to re-commence replacement therapy, as determined by clinician”. |
| “...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... The ESC also noted that no re-assessment period was stipulated, and no definition of what constituted a break in therapy was proposed.” (Paragraphs 2.4 and 7.4) | Not addressed. |
| “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.” (Paragraphs 6.9 and 7.4) | Not included in restriction. Resubmission claimed “This has not been incorporated in the criteria because treating other deficiencies and illnesses are considered as standard care” (p5). |
| “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.” (Paragraphs 6.9 and 7.4) | “The timeframe for clinical reassessment was set at 12 months (ie, 2 scripts, each with 5 repeats).” (p5) |
| No requirement for response to be measured over time (not just in relation to baseline). This is in contrast to the Holdaway 2015 study, which considered response in relation to both baseline measurements, and treatment over time. e.g. a patient discontinued treatment if, once stable on treatment, they experienced a deterioration in QoL-AGHDA score >5 on two measurements more than 6 months apart (without explanation by coincidental illness or stress). (Paragraph 6.8, Table 4). The proposed PBS criteria considered response to treatment in relation only to baseline QoL-AGHDA score. “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.” (Paragraph 6.9) | Resubmission argued that “it would penalise those patients with a large response in the first 12 months of treatment; those patients could still show an improvement in their QoL, but the relative deterioration over time might penalise them compared to patients with a lower initial response” (p5). The resubmission did not provide an explanation for why a patient taking somatropin would experience a decline in their QoL over time. The PSCR for the November 2016 submission argued that 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. (PSD, November 2016, paragraph 6.34). |
| “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.” (Paragraph 6.9) | Resubmission interpreted this as a PBAC recommendation to amend the continuing restriction (i.e. “Patient must not have experienced major treatment-related adverse side effects”). The ESC advice was a comment on the data presented in Holdaway, not specifically a concern with the proposed PBS restriction. |

Source: Compiled by the PBAC Secretariat. Paragraph references refer to the November 2016 somatropin minutes.

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

4 Population and disease

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 Adults with GHD have substantially impaired QoL due to, among other symptoms, mood fluctuations, anxiety, depression, fatigue and lack of strength.
- 4.3 As per the November 2016 resubmission, the current resubmission proposed the use of QoL scores assessed using the quality of life assessment of growth hormone deficiency in adults (QoL-AGHDA) instrument for treatment initiation, continuation and recommencement.

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

5 Comparator

- 5.1 The previous major resubmission considered by the PBAC in November 2016 nominated standard care as the main comparator. This was unchanged in the current resubmission. The PBAC previously considered this to be appropriate (PSD, November 2016, paragraph 7.5).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item. However, the PBAC recalled that for its November 2016 consideration of somatropin for adults with GHD it received substantial 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 weight loss and 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 self-funding the treatment over many years.

Clinical trials

- 6.3 No new clinical data was presented in the minor resubmission. The clinical evidence presented in the November 2016 resubmission addressed the QoL impairments of

GHD only. As noted in Table 1, the PBAC deferred its November 2016 recommendation in order to seek further comparative analysis on the range of clinical benefits provided by somatropin, among other matters.

6.4 The basis of the minor resubmission's request was a discussion on:

- the effects of somatropin on body composition, bone mineral density, cardiovascular risk, and cardiorespiratory function;
- safety; and
- various QoL assessment instruments, including the QoL-AGHDA

(largely based on an unpublished qualitative review by Lipworth et al, (March 2014), *Report summarising outcomes of preliminary ESA/APEG working group analysis*).

Comparative effectiveness

6.5 The narrative review of evidence in the minor resubmission made the following conclusions:

- **Body composition:** "The analysis shows overwhelming evidence that GH replacement brings beneficial changes in fat and lean mass regardless of the severity of GH deficiency."
- **Bone mineral density:** "All studies which have followed treatment effects for at least 5 years duration report a progressive increase in bone mineral density in GH deficient adults... as highlighted in the ESA/APEG report. Although these are uncontrolled studies, findings are significant because the changes are opposite to the natural decline in bone density in adulthood."
- **Cardiovascular risk:** "These results provide strong evidence that GH replacement reduces cardiovascular risk markers with components improving in a variable and time-dependent manner."
- **Cardiorespiratory function:** "The results provide strong evidence that GH replacement therapy improves cardiorespiratory function in adults with GHD."

6.6 The resubmission also provided a discussion on various QoL instruments, including the QoL-AGHDA. The resubmission reiterated that the factors that contribute to the QoL of an adult with GHD include a wide range of emotional, cognitive and social functioning areas and that generic QoL assessment tools are likely to miss important aspects of the patients' experience of the disease, consequently reducing reliability and responsiveness. The QoL-AGHDA is the only disease-specific instrument that has been developed. This instrument has been adopted in the UK and New Zealand as part of the criteria for funding GH treatment.

Comparative harms

6.7 The safety evidence remained unchanged from the previous major resubmission considered in November 2016.

- 6.8 The November 2016 resubmission stated that no serious adverse events 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 had noted that the exit criteria in the study included “for major adverse side effects”.
- 6.9 The Pre-PBAC Response to this minor resubmission argued that “The reported 17% of withdrawals from treatment [in Holdaway et al. (2015)] were due to patients’ decision to stop treatment, patients lost to follow-up, patients emigrating from New Zealand and, in a minority of patients, their treatment failing to achieve appropriate improvement in quality of life (QoL) via QoL-AGHDA scores.”
- 6.10 The minor resubmission claimed that, “Historically higher weight-based doses of GH were used to treat adults with GHD. Therefore it is likely that the dose-related adverse events reported in these earlier randomised trials greatly overestimate the frequency compared with current clinical practice of dose titration to mid reference range IGF-1 concentrations”.

Clinical claim

- 6.11 The November 2016 resubmission claimed that somatropin is superior in terms of comparative effectiveness with respect to QoL and noninferior in terms of comparative safety over standard care. 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 and was likely overestimated. The PBAC considered that the claim of noninferior 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 [July 2011] 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. (PSD, November 2016, paragraphs 7.7-7.8).
- 6.12 The minor resubmission claimed superior comparative effectiveness of somatropin compared with BSC. Specifically, it claimed that, “GH replacement improves body composition, cardiorespiratory function, metabolic status and QoL in adult patients with severe GHD. These improvements occur in a time-dependent manner with the level of evidence supporting the benefits dictated by the duration of controlled evaluation that was deemed practical and ethical for an injection therapy. The evidence from open label studies that GH improves strength, bone mineral density and metabolic risk profile is strong because the changes are opposite to those expected to occur with aging.”

- 6.13 In terms of comparative safety of somatropin, the minor resubmission claimed that, “aside from issues arising from product impurities, side effects do not arise with hormone replacement therapy of an appropriate replacement dose” (pp8-9).
- 6.14 Consistent with its previous views, the PBAC considered that the claim of superior comparative effectiveness was reasonable, but the claim of noninferior comparative safety was not adequately supported by the data. The PBAC considered that the comparative effectiveness of somatropin may have been overestimated but this was difficult to quantify.

Economic analysis

- 6.15 As a minor resubmission, there was no economic comparison presented.
- 6.16 The major resubmission considered by PBAC in November 2016 presented a stepped cost-utility analysis using a Markov model comparing somatropin with BSC, resulting in \$15,000/QALY - \$45,000/QALY gained. The ICER was 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/QALY - \$45,000/QALY gained to \$45,000/QALY – \$75,000/QALY gained (November 2016 PSD, paragraph 6.49).
- 6.17 In November 2016, the PBAC noted that several issues introduced uncertainty to the ICER calculations, including that Holdaway et al. (2015) data contained no untreated patients and was thus likely to be highly selective of patients treated with somatropin. In addition, the requested PBS criteria included re-treatment, but the costs and benefits associated with re-treatment were excluded from the economic model and financial estimates in the previous resubmission. (PSD, November 2016, paragraph 6.45) Given the high uncertainty in quantifying the clinical benefit of somatropin treatment, the PBAC considered that a reduction in drug cost would improve the cost-effectiveness in this setting. (PSD, November 2016, paragraph 7.9).
- 6.18 The minor resubmission did not address these issues. However, the PBAC considered that its uncertainty in the model would be mitigated, and the cost-effectiveness of somatropin would be acceptable, at an ICER of no more than \$15,000 per QALY gained, calculated using the November 2016 model. The November 2016 model base case assumed a >6 point QoL-AGHDA score improvement between 6 and 12 months, and a 13 point improvement from 12 months onwards.
- 6.19 Using the price per milligram for somatropin required to achieve a base case ICER of no more than \$15,000 per QALY gained, the PBAC noted that the ICER would be around \$15,000/QALY - \$45,000/QALY gained or less if the improvement in QoL-AGHDA were reduced to the minimum amount required to continue treatment with somatropin in:
- the November 2016 proposed PBS restriction (of ≥ 8 points within the first year of treatment, ≥ 6 points thereafter);

- the current proposed restriction (of >7 points from 12 months onwards); and
- an alternative criterion (>7 points from 6 months onwards).

Drug cost/patient/year: \$ [REDACTED] for females and \$ [REDACTED] for males.

6.20 The drug cost is unchanged, with the minor resubmission noting that ESA/APEG do not set the price of somatropin. The costs calculated during the November 2016 major resubmission assumed a dispensed cost per milligram for somatropin of \$ [REDACTED]. Treatment is administered daily, on an ongoing basis. With a mean dose per day of 0.45 mg for females, and 0.31 mg for males, the annual treatment cost for females is \$ [REDACTED] ($=0.45\text{mg} \times 365 \times \$ [REDACTED]$), and for males is \$ [REDACTED] ($=0.31\text{mg} \times 365 \times \$ [REDACTED]$).

Estimated PBS usage & financial implications

- 6.21 In November 2016, the PBAC considered that the utilisation and financial impact estimates in the major resubmission 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, albeit informed by epidemiological data from the United Kingdom and New Zealand. The PBAC further considered that the November 2016 major resubmission used an inconsistent and unclear approach to the estimated PBS usage and financial implications, resulting in uncertainties. The PBAC also considered that addressing some of the issues with the PBS restriction may reduce some uncertainty. (PSD, November 2016, Paragraph 7.10).
- 6.22 The minor resubmission did not provide an update to the financial estimates and stated that “The financial impact will be modest, with an estimated cost to the PBS of less than \$10 million per year in a high unmet need patient population with no alternative treatments available” (p18).

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of somatropin for the treatment of adults with severe GHD, and substantially impaired QoL at baseline, on the basis that it should be available only under special arrangements under Section 100 (Growth Hormone Program). The PBAC is satisfied that somatropin provides, for some patients, a significant improvement in efficacy over standard care.
- 7.2 The PBAC recalled its November 2016 decision to defer making a recommendation on whether to list somatropin on the PBS for adults with severe GHD. It had 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. The PBAC had considered that a reduction in drug cost would address some of the uncertainty in the cost-effectiveness of somatropin in this setting.

7.3 In terms of the PBS restriction, the PBAC recalled its previous concerns, and noted the applicant's proposed refinements (paragraph 3.1 and Table 5). The PBAC noted that the restrictions presented in the resubmission required reformatting to comply with requirements of PBS listings. The PBAC recommended a Written Authority Required listing, and also recommended:

- a maximum quantity of one, with five repeats, to allow for six months' supply on initial, continuing and re-commencement of treatment phase prescriptions. The PBAC considered it appropriate that a patient should be reviewed by their clinician every six months (not 12 months as proposed by the minor resubmission).
- the inclusion of Prescriber Instructions to limit any increases to the maximum quantity to one months' supply.
- the inclusion of Administrative Advice that, "No increase in the maximum number of repeats may be authorised," to limit supply to six months.
- specific supporting information be provided at the time of initial and re-commencement of treatment written application, including evidence of meeting the clinical eligibility criteria, and a baseline serum IGF-measurement less than three months' old.
- supporting evidence be required to access continuing therapy.
- for the continuation and re-commencement of treatment phase listing, a patient must have previously received PBS-subsidised therapy with this drug for this condition when the patient was aged 18 years or older.
- it would be appropriate for patients who had been previously treated as an adult with PBS-subsidised somatropin, to take a break in therapy and then re-commence, providing that the patient's previous treatment had not lapsed due to a failure to maintain IGF-1 levels within the normal range for age and sex .
- that initial and re-commencement of treatment must be prescribed by an endocrinologist, and continuation of treatment must be prescribed by, or in consultation with, an endocrinologist.
- that it was unnecessary to include a clinical criterion that patients must not have experienced major adverse events while receiving therapy, as prescribers are unlikely continue prescribing therapy under these

circumstances.

- there were no specific clinical or cost-effectiveness reasons to include any dosing arrangements on the somatropin listings for adults with severe GHD.

- 7.4 The PBAC noted that it was still unclear how a patient who has previously been treated with somatropin, as a child for GHD and/or by self-funding as an adult, would qualify for treatment under the recommended listing as they may not be able to meet the eligibility criteria for substantially impaired QoL at baseline.
- 7.5 The PBAC noted that there are five sponsors of forms of PBS-listed somatropin with TGA registration for the treatment of adults with severe GHD, and that the PBAC recommendation would only apply to these products.
- 7.6 The PBAC recalled its previous view that there was a clinical place for somatropin in the treatment of adults with severe GHD. The PBAC noted the narrative review of evidence in relation to the effects of somatropin on body composition, bone mineral density, cardiovascular risk, cardiorespiratory function, safety and various QoL assessment instruments. Although non-comparative, the PBAC nonetheless found that this evidence supported its previous findings concerning the clinical need and benefit of this therapy.
- 7.7 The PBAC noted that the nominated comparator of standard care was unchanged in the current resubmission. The PBAC again considered this to be appropriate.
- 7.8 Consistent with its previous views, the PBAC considered that the claim of superior comparative effectiveness was reasonable, but the claim of noninferior comparative safety was not adequately supported by the data. The PBAC considered that the comparative effectiveness of somatropin remained difficult to quantify and likely overestimated. The PBAC also recalled its previous advice [July 2011 PSD] that somatropin was inferior in terms of short-term safety compared to placebo, but reiterated its view that higher treatment doses in earlier studies may have influenced this result.
- 7.9 The PBAC noted that as a minor resubmission, no new economic comparison was presented. Thus, the PBAC maintained its concerns regarding the November 2016 model inputs, which had introduced uncertainty into the ICER calculations. However, the PBAC also recalled its view that given the high uncertainty in quantifying the clinical benefit of somatropin treatment, a reduction in drug cost would likely improve the cost-effectiveness of somatropin in this setting. The PBAC therefore advised that its uncertainty would be mitigated, and the cost-effectiveness of somatropin in this setting would be acceptable, at a lower ICER (see paragraph 6.18).
- 7.10 In terms of the estimated utilisation and financial estimates, the PBAC recalled its previous view that these were likely underestimated in the November 2016 resubmission, noting the subjective self-assessment inherent in the QoL-AGHDA. However, the PBAC also recalled that it had considered that clarifying the PBS restriction may reduce the uncertainty of the estimates. In this regard, the PBAC noted the changes made by the sponsor and in the recommended listing (as

discussed in paragraph 7.3). Moreover, the PBAC considered that it was unlikely that patients who do not receive a benefit from somatropin would continue with a treatment involving a daily injection.

- 7.11 The PBAC noted this listing requires a complex written restriction, which will require consultation with the Department of Human Services and affected sponsors.
- 7.12 The PBAC advised that somatropin is not suitable for prescribing by nurse practitioners.
- 7.13 The PBAC recommended that the Early Supply Rule should not apply.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review. Independent review is not available where the PBAC makes a positive recommendation

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new indication (restriction to be finalised).

9 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.

10 Sponsor's Comment

The Endocrine Society of Australia and Australian Paediatric Endocrine Group are thrilled the PBAC recommended somatropin for the treatment of adults with severe GHD and substantially impaired QoL at baseline.