PUBLIC SUMMARY DOCUMENT

Product: Somatropin (Recombinant human growth hormone), injection, 5 mg (15 i.u.) and 12 mg (36 i.u.) in 1 mL cartridge (with preservative), Genotropin®; powder for injection, 5 mg (15 i.u.) and 12 mg (36 i.u.) with diluent in pre-filled pen (with preservative), Genotropin GoQuick®; injection, 0.6 mg (1.8 i.u.), 0.8 mg (2.4 i.u.), 1 mg (3 i.u.), 1.2 mg (3.6 i.u.), 1.4 mg (4.2 i.u.), 1.6 mg (4.8 i.u.), 1.8 mg (5.4 i.u.), and 2 mg (6 i.u.) with diluent in single use syringe (without preservative), Genotropin MiniQuick®

Sponsor: Pfizer Australia Pty Ltd

Date of PBAC Consideration: July 2011

1. Purpose of Application

The submission requested an extension of the current Section 100 (Human Growth Hormone Program) listing to include treatment of severe adult growth hormone deficiency (AGHD).

2. Background

Somatropin has been subsidised through PBS under the Section 100 Human Growth Hormone Program, in accordance with the 'Guidelines for the Availability of Human Growth Hormone (hGH) as a Pharmaceutical Benefit' since August 1993.

At the March 2008 meeting, the PBAC recommended amending the listing of Genotropin branded somatropin products to include improvement of body composition and short stature associated with Prader-Willi Syndrome (PWS) in patients up to 18 years of age on the basis of high but acceptable cost-effectiveness compared with placebo. Listing was effective 1 July 2009.

In September 2010, new "Guidelines for the Pharmaceutical Benefits Scheme Growth Hormone Program" took effect which are an amalgamation of the 'Guidelines for the Availability of Human Growth Hormone (hGH) as a Pharmaceutical Benefit (July 2008)' and the 'Guidelines for the Availability of Human Growth Hormone (hGH) as a Pharmaceutical Benefit for the treatment of Prader-Willi Syndrome (February 2009)'.

3. Registration Status

Genotropin brand of somatropin is TGA registered for the following indications:

- Short stature due to decreased or failed secretion of pituitary growth hormone;
- **Treatment of adults with severe growth hormone deficiency as diagnosed in the insulin tolerance test for growth hormone deficiency and defined by peak growth hormone concentrations of less than 2.5 nanogram/mL;**
- Growth disturbances associated with gonadal dysgenesis (Turner's syndrome);
- Improvement of body composition and treatment of short stature associated with Prader-Willi syndrome (PWS) in paediatric patients;
- For treatment of growth disturbance in children with chronic renal insufficiency whose height is on or less than twenty-fifth percentile and whose growth velocity is on or less than twenty-fifth percentile for bone age. Chronic renal insufficiency is defined as glomerular filtration rate of less than 50 mL/min/1.73m^2.

4. Listing Requested and PBAC's View

The submission proposed to extend the current Section 100 (Human Growth Hormone Program) criteria for availability to read as follows, with the requested listing shown in bold:

"Genotropin branded products are also available for the treatment of Prader-Willi Syndrome **and for the treatment of adults with severe growth hormone deficiency** in accordance with the 'Guidelines for the Pharmaceutical Benefits Scheme Growth Hormone Program".

The submission proposed that further details of the proposed criteria for availability would be contained in the "Guidelines for the Pharmaceutical Benefits Scheme Growth Hormone Program". The submission proposed the following eligibility criteria for inclusion in the Guidelines:

Proposed restriction for initiation of treatment with Genotropin for adult growth hormone deficiency (AGHD)

Aetiology of disease	Proposed eligibility criteria

Adults with severe growth hormone deficiency with onset in childhood (of organic or idiopathic origin)	X.X.1 Eligibility criteria
	Adults with a history of severe growth hormone deficiency in childhood who have:
	• ceased treatment with growth hormone for at least 4 weeks prior to re-testing for persistent growth hormone deficiency; OR
	• never received growth hormone therapy; AND
	• ongoing severe growth hormone deficiency defined as peak growth hormone concentrations of less than 2.5 µg/L:
	  • measured by an insulin tolerance test (or other provocative test where an insulin tolerance test is not indicated); OR
	  • ≥3 pituitary hormone deficiencies and an IGF-1 level below the age-specific reference range; AND
	• health-related quality of life score of at least 15, measured by the QoL-AGHDA instrument, prior to initiating or restarting growth hormone therapy

Adults with severe growth hormone deficiency with onset in adulthood	X.X.1 Eligibility criteria
	Adults who have:
	• ongoing severe growth hormone deficiency defined as peak growth hormone concentrations of less than 2.5 µg/L:
	  • measured by an insulin tolerance test (or other provocative test where an insulin tolerance test is not indicated); OR
	  • ≥3 pituitary hormone deficiencies and an IGF-1 level below the age-specific reference range; AND
	• health-related quality of life score of at least 15, measured by the QoL-AGHDA instrument, prior to initiating growth hormone therapy

Abbreviations: IGF-I, insulin-like growth factor 1; ng, nanogram; mL, millilitres; QoL-AGHDA, Quality of Life Assessment of Growth Hormone Deficiency in Adults

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Growth hormone is released into the circulation from the anterior pituitary gland to elicit various known biological actions in many cell types and tissues. Adults with growth hormone deficiency have impaired health, including abnormal body composition, reduced

physical fitness, increased cardiovascular risk factors, osteopaenia and impaired psychological function.

The submission proposed that the listing of Genotropin branded somatropin would provide a subsidised treatment option for severe AGHD patients with impaired quality of life.

6. Comparator

The submission nominated standard care (SC), which consists of regular monitoring by an endocrinologist, medical management of signs and symptoms and management of risk factors arising from AGHD as appropriate, as the main comparator.

The PBAC considered this appropriate.

7. Clinical Trials

The submission presented 39 randomised controlled trials comparing somatropin with placebo in patients with AGHD. The PBAC noted that an impaired QoL at baseline was not an entry criterion for the trials, which limited the applicability of these trials to the requested listing for patients with impaired QoL as measured by the quality of life assessment for growth hormone deficiency in adults (QoL-AGDHA) instrument. The PBAC additionally noted that the trials presented in the submission used various QoL instruments and that only two of the trials used the instrument of QoL-AGHDA used in the proposed restriction.

The submission used body composition outcomes (lean body mass - LBM and fat mass - FM) as supportive outcomes. The submission presented meta-analyses for Nottingham Health Profile (NHP) (6 trials for total score, 15 trials for part-scores), Psychological General Well-Being Index (PGWB) (8 trials), LBM (17 trials for change, 5 trials for percentage change) and FM (20 trials).

It was noted that the trials presented had high risk of bias, including uncertain blinding, post-randomisation selection bias and high risk of outcomes reporting bias. In general, randomisation was either not clearly reported or by third-party randomisation. All trials were reported to be double-blind, however not all publications described whether outcome assessors were blinded. The submission described that the patient populations in which the analyses were undertaken included intention to treat, per protocol or other analyses. In general there was limited information on how the trials dealt with missing data. As many publications and study reports were more than 10 years old, limited information was available on the trial methodology, and therefore it was uncertain whether bias may have been introduced in the trials.

The published trials presented in the submission are shown in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Cuneo et al.	The Australian multicenter trial of growth hormone (GH) treatment in GH- deficient adults.	*J Clin Endocrinol Metab* 1998; 83(1):107-116

Chihara et al. (2004)	Adult GH deficiency in Japanese patients: Effects of GH treatment in a randomised, placebo-controlled trial.	*Eur J Endocrinol* 2004; 151(3):343-350
Urushihara et al.	Heterogeneity in responsiveness of perceived quality of life to body composition changes between adult- and childhood-onset Japanese hypopituitary adults with GH deficiency during GH replacement.	*Eur J Endocrinol* 2007; 156(6):637-645
Shimatsu A et al.	Growth hormone deficiency and replacement therapy in Japan: Results of placebo-controlled double-blind study and open-label extension study. A Decade of HypoCCS: The Changing Face of Pituitary Disease.	*BioScientifica Ltd, Bristol;* 2008; 171-81
Chihara et al. (2006a)	Efficacy and safety of growth hormone (GH) in the treatment of adult Japanese patients with GH deficiency: A randomised, placebo-controlled study.	*Growth Horm IGF Res* 2006a;16(2):132-142
Chihara et al. (2006b)	Effect of growth hormone treatment on trunk fat accumulation in adult GH-deficient Japanese patients: A randomised, placebo-controlled trial.	*Curr Med Res Opin* 2006b; 22(10):1973-1979
Chihara et al. (2006c)	Growth hormone (GH) effects on central fat accumulation in adult Japanese GH deficient patients: 6-month fixed-dose effects persist during second 6-month individualized-dose phase.	*Endocr J* 2006c; 53(6):853-858
Chihara et al. (2008)	Efficacy and safety of individualized growth hormone treatment in adult Japanese patients with growth hormone deficiency.	*Growth Horm IGF Res* 2008; 18(5):394-403
Chihara et al. (2010)	Dose-dependent changes in body composition during growth hormone (GH) treatment in Japanese patients with adult GH deficiency: A randomized, placebo-controlled trial.	*Growth Horm IGF Res* 2010; 20(3):205-211
Christ et al. (2004)	Effects of growth hormone (GH) replacement therapy on low-density lipoprotein apolipoprotein B100 kinetics in adult patients with GH deficiency: A stable isotope study.	*J Clin Endocrinol Metab* 2004; 89(4):1801-1807
Christ et al. (1999)	Effects of Growth Hormone (GH) Replacement Therapy on Very Low Density Lipoprotein Apoliproprotein B100 Kinetics in Patients with Adult GH Deficiency: A stable isotope study.	*J Clin Endocrinol Metab* 1999; 84:307-316
Engstrom et al.	Effects of Growth Hormone (GH) on Ghrelin, Leptin, and Adiponectin in GH-Deficient Patients.	*J Clin Endocrinol Metab* 2003; 88(11):5193-5198.
Burman et al. (1997)	Growth hormone (GH)-deficient men are more responsive to GH replacement therapy than women.	*J Clin Endocrinol Metab* 1997; 82(2):550-555.
Burman et al. (1995)	Quality of life in adults with growth hormone (GH) deficiency: Response to treatment with recombinant human GH in a placebo-controlled 21-month trial.	*J Clin Endocrinol Metab* 1995; 80(12):3585-3590.
Ezzat et al.	Gender-specific responses of lean body composition and non-gender-specific cardiac function improvement after GH replacement in GH-deficient adults.	*J Clin Endocrinol Metab* 2002; 87(6):2725-2733.

Florkowski et al. (1996)	Low-dose growth hormone replacement lowers plasma leptin and fat stores without affecting body mass index in adults with growth hormone deficiency.	*Clin Endocrinol* 1996; 45(6):769-773
Florkowski et al. (1998)	Growth hormone replacement does not improve psychological well-being in adult hypopituitarism: A randomized crossover trial.	*Psychoneuroendocrinology* 1998; 23(1):57-63
Hoffman et al.	Growth Hormone (GH) Replacement Therapy in Adult-Onset GH Deficiency: Effects on Body Composition in Men and Women in a Double-Blind, Randomized, Placebo-Controlled Trial.	*J Clin Endocrinol Metab* 2004; 89(5):2048-2056
Hwu et al.	Growth hormone (GH) replacement reduces total body fat and normalizes insulin sensitivity in GH-deficient adults: A report of one-year clinical experience.	*J Clin Endocrinol Metab* 1997; 82(10):3285-3292
Johannsson et al.	The individual responsiveness to growth hormone (GH) treatment in GH- deficient adults is dependent on the level of GH-binding protein, body mass index, age, and gender.	*J Clin Endocrinol Metab* 1996; 81(4):1575-1581
Jorgensen et al.	Growth hormone versus placebo treatment for one year in growth hormone deficient adults: Increase in exercise capacity and normalization of body composition.	*Clin Endocrinol* 1996; 45(6):681-688
Mahajan et al.	Atypical depression in growth hormone deficient adults, and the beneficial effects of growth hormone treatment on depression and quality of life.	*Eur J Endocrinol* 2004; 151(3):325-332
Mesa et al.	Growth hormone deficiency in adults: Effects of replacement therapy on body composition and health-related quality of life.	*Med Clin* 2003; 120(2):41-46
Oertel et al.	The effect of growth hormone substitution on cognitive performance in adult patients with hypopituitarism.	*Psychoneuroendocrinology* 2004; 29(7):839-850
Rodriguez-Arnao et al.	Effects of growth hormone replacement on physical performance and body composition in GH deficient adults.	*Clin Endocrinol* 1999; 51(1):53-60
Sneppen et al.	Bone mineral content and bone metabolism during physiological GH treatment in GH-deficient adults - An 18-month randomised, placebo-controlled, double blinded trial.	*Eur J Endocrinol* 2002; 146(2):187-195
Snyder et al.	Effect of growth hormone replacement on BMD in adult-onset growth hormone deficiency.	*J Bone Miner Res* 2007; 22(5):762-770
Soares et al.	Impact of recombinant human growth hormone (RH-GH) treatment on psychiatric, neuropsychological and clinical profiles of GH deficient adults: A placebo-controlled trial.	*Arq Neuro-Psiquiatr* 1999; 57(2 A):182-189
Underwood et al.	Growth Hormone (GH) Dose-Response in Young Adults with Childhood-Onset GH Deficiency: A Two-Year, Multicenter, Multiple-Dose, Placebo-Controlled Study.	*J Clin Endocrinol Metab* 2003; 88(11):5273-5280
Verhelst et al.	Two years of replacement therapy in adults with	*Clin Endocrinol* 1997; 47(4):485-494

	growth hormone deficiency.	
Wallymahmed et al.	Quality of life, body composition and muscle strength in adult growth hormone deficiency: The influence of growth hormone replacement therapy for up to 3 years.	*Clin Endocrinol* 1997; 47(4):439-446
Weaver et al.	The effect of low dose recombinant human growth hormone replacement on regional fat distribution, insulin sensitivity, and cardiovascular risk factors in hypopituitary adults.	*J Clin Endocrinol Metab* 1995; 80(1):153-159
Woodhouse et al.	Measures of submaximal aerobic performance evaluate and predict functional response to growth hormone (GH) treatment in GH-deficient adults.	*J Clin Endocrinol Metab* 1999; 84(12):4570-4577
Meta-analyses of direct randomised trials		
Arwert et al.	The influence of growth hormone (GH) substitution on patient-reported outcomes and cognitive functions in GH-deficient patients: A meta-analysis.	*Growth Horm IGF Res* 2005; 15(1):47-54
Bryant et al.	Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: A systematic review and economic evaluation.	*Health Technol Assess* 2002; 6(19)
Deijen et al.	Differential effect sizes of growth hormone replacement on quality of life, well-being and health status in growth hormone deficient patients: A meta-analysis.	*Health Qual Life Outcomes* 2005; 3
Fassbender et al.	Treatment of proven growth hormone deficiency in adults with recombinant human growth hormone according to evidence-based criteria.	*Dtsch Med Wochenschr* 2005; 130(45):2589-2595
Maison et al.	Impact of Growth Hormone (GH) Treatment on Cardiovascular Risk Factors in GH-Deficient Adults: A Metaanalysis of Blinded, Randomized, Placebo-Controlled Trials.	*J Clin Endocrinol Metab* 2004; 89(5):2192-2199
Mardh et al.	Growth Hormone Replacement Therapy in Adult Hypopituitary Patients with Growth Hormone Deficiency: Combined Data from 12 European Placebo Controlled Clinical Trials.	*Endocrinol Metab Suppl* 1994; 1:43-49

8. Results of Trials

Quality of life outcomes

The PBAC noted the meta-analysis presented in the submission of trials reporting the Nottingham Health Profile (NHP) score did not result in a statistically significant improvement in the total NHP score nor any of the sub scores (unweighted and weighted) for somatropin. The PBAC also noted the meta-analysis of trials using PGWB reported a statistically significant increase in the total score and the components of positive well-being and vitality compared to placebo treatment. However the clinical significance of an improvement of one to four points on the 110 point PGWB scale was unclear. Additionally the PBAC noted that two trials (Hoffman 2004 and Underwood 2003), which were excluded from the PGWB meta-analysis because detailed data were not available in the publications, reported that treatment with somatropin resulted in no significant change in QoL using a number of assessment tools including the PGWB, and that inclusion of these trials in the PGWB meta-analysis may have resulted in the difference in PGWB scores no longer reaching statistical significance. The PBAC also

noted that the two trials that assessed QoL using the QoL-AGHDA did not present details about baseline values and improvement, but both reported no significant effect of treatment with somatropin.

The table below presents the results of disease specific QoL instruments used in the clinical trials.

Results for disease specific quality of life instruments

Trial ID	Somatropin		Placebo		Mean difference (SOM−PBO)
	N	endpoint - baseline	N	endpoint - baseline	
QoL-AGHDA					
Chihara 2006a	37	NR	36	NR	No significant treatment effects reported (p=0.5588)
Mesa 2003	85	NR	80	NR	No significant treatment effects reported
DSQ					
Florkowski 1998	10	NR	10	NR	No significant treatment effects reported

NR = not reported; SOM = somatropin; PBO = placebo; QoL-AGHDA = Quality of Life Assessment of Growth Hormone Deficiency in Adults; DSQ = Disease Specific Questionnaire

Florkowski 1998 reported that somatropin treatment did not result in statistically significantly better treatment effects using the disease specific questionnaire (DSQ) compared to placebo treatment. Another unpublished study did not demonstrate statistically significant improvement in the growth hormone deficiency questionnaire (GHDQ) score for somatropin. The submission noted that none of the trials were restricted to patients with impaired QoL at baseline.

Body composition outcomes

Somatropin resulted in a statistically significant increase in LBM and a statistically significant decrease in FM compared to placebo. The mean difference in LBM was 2.3 kg (95% CI: 1.7, 2.9) and the mean difference in FM was -2.6 kg (95% CI: -3.0, -2.1). There were differences in methodology of measuring LBM and FM between the trials, including duration of the trial and patient characteristics, which may have explained the heterogeneity observed in the meta-analyses. The submission did not discuss whether the changes in LBM and FM were clinically relevant, and did not provide a minimum clinical important difference. As most trials were six months in duration the sustainability of the differences in body composition was uncertain. Two trials were of 2 years in duration, Snyder 2007 and Underwood 2003. Both trials reported no statistically significant difference in FM, while for LBM, Snyder 2007 reported no statistically significant difference, and Underwood 2003 reported a statistically significant difference.

The submission did not provide meta-analyses of the safety outcomes of the 39 included trials, as safety outcomes were not consistently reported across the trials. The submission presented adverse events from the clinical trial reports combined, for an unpublished study separately and a summary of adverse events reported in publications. Somatropin appeared to be associated with more adverse events than placebo treatment. The most common adverse events were oedema, musculoskeletal pain/stiffness and athralgias (non-inflammatory joint pain). The submission stated that the adverse events were in general

mild and these patients recovered either spontaneously or after dose reductions, stating that of those trials that reported somatropin dose reductions due to oedema and joint pain, approximately 36% to 60% of the patients had complete recovery.

The submission provided additional data on potential safety concerns beyond those identified in the clinical trials from the Australian Product Information (PI), the open-label period of the clinical trials, the Periodic Safety Update Report (PSUR) up to March 2009, and two observational studies KIMS (Pfizer International Metabolic Database) and HypoCSS (Hypopituitary Control and Complications Study).

The submission stated that the frequency of adverse events reported in the open-label extension phase appeared to be similar to the double-blind period, with the exception of upper respiratory tract infection which appeared to be increased in most clinical trial reports (7.8% in double blind period; 38.1% in open-label extension period).

The most common adverse events reported in the observational study KIMS were arthralgia, influenza-like symptoms, upper respiratory tract infection and headache.

The submission did not present an extended assessment of adverse events in other patients groups, such as children, treated with somatropin.

9. Clinical Claim

The submission described somatropin as superior in terms of comparative effectiveness (improvement in QoL and body composition) and inferior in terms of comparative safety over placebo.

The PBAC considered the clinical benefit of somatropin was uncertain. The PBAC accepted the submission's claim that somatropin is inferior in terms of short-term safety to placebo. The PBAC considered that the long-term safety of somatropin is uncertain.

10. Economic Analysis

The submission presented a stepped economic evaluation based on data from a subgroup analysis of the KIMS observational study in AGHD patients.

The economic model was a semi-Markov cohort model with three health states: 1) on treatment, 2) discontinue treatment, and 3) death. In the somatropin arm of the model patients started in the on-treatment health state and could remain in this health state, discontinue treatment or die. For the patients who discontinue treatment, the QoL-AGHDA scores returned immediately to baseline values. Once a somatropin patient discontinued treatment, there was no possibility to restart treatment. This assumption may not have been valid, as the requested listing included a reference that patients can restart somatropin treatment for AGHD. For placebo treatment, patients started in the discontinue treatment state and could stay in this state or transition to the death state. The cycle length in the model was one month, and a half cycle correction was included. The duration of the model was five years. This may not be not appropriate as AGHD is a life-long disease and the submission did not propose any discontinuation criteria, so it was assumed that treatment would be chronic. The model did not assume any waning of efficacy for somatropin over time.

The submission estimated that the ICER for somatropin was in the range of $45,000 - $75,000/QALY. The PBAC considered that the ICER for somatropin compared to placebo treatment was likely to be higher than the specific figure arrived at in the submission because the submission may have:

- underestimated the incremental cost:
  - the daily dose of somatropin may have been underestimated;
  - costs for the treatment of adverse events have been excluded; and
  - costs of increased monitoring (thyroid function and glucose tolerance) were excluded;
- overestimated the QALY gain for somatropin:
  - the QoL-AGHDA results were derived from an observational database (KIMS) which
    - included very few untreated patients to act as a control arm;
    - may have had selection bias of included patients;
    - may have had reporting bias, as follow-up beyond baseline was limited, due to underreporting and/or discontinuation due to lack of efficacy (e.g. at 1 year only 48% of patients had an QoL-AGHDA assessment decreasing to 4% of patients at year 5;
  - the model assumed that 75% of the efficacy of that estimated at one year is already achieved after only two weeks of treatment; and
  - the transformation equation from QoL-AGHDA to utility value, including age and sex as variables, had a R^2=0.36, indicating uncertainty surrounding the transformation step, and was based on mapping from a general population survey.

Varying the QoL-AGHDA initiation criteria changed the ICER, with higher inclusion criteria resulting in lower ICERs. The submission did not present an analysis including all patients with severe AGHD (i.e. without the requirement for impaired QoL). This may not be appropriate as somatropin improved body composition at six months in clinical trials which may result in leakage to patients with normal QoL.

As there was uncertainty surrounding the efficacy of somatropin in improving QoL, a sensitivity analysis was performed during the evaluation, reducing the efficacy by 50% at each time point. This may have reflected the bias in the observational database, with underreporting of QoL-AGHDA for patients who do not achieve a reduction.

The results of the sensitivity analyses indicated that the model was most sensitive to treatment efficacy and the somatropin dose. The model was to a lesser extent sensitive to the uncertainty surrounding the transformation of QoL-AGHDA to utilities.

For PBAC's views, see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the total net cost to the PBS to be less than $10 million year 5.

12. Recommendation and Reasons

The PBAC considered the comparator of standard care, consisting of regular monitoring by an endocrinologist, medical management of signs and symptoms, and management of risk factors arising from adult growth hormone deficiency (AGHD), appropriate.

The submission presented 39 randomised controlled trials comparing somatropin with placebo in patients with AGHD with a normal quality of life (QoL). The PBAC noted that an impaired QoL at baseline was not an entry criterion for the trials, which limited the applicability of these trials to the requested listing for patients with impaired QOL as measured by the QoL-AGDHA instrument. The PBAC additionally noted that the trials presented in the submission used various QoL instruments and that only two of the trials used the instrument of QoL-AGHDA used in the proposed restriction.

The PBAC noted the meta-analysis presented in the submission of trials reporting the Nottingham Health Profile (NHP) score did not result in a statistically significant improvement in the total NHP score nor any of the sub scores (unweighted and weighted) for somatropin. The PBAC also noted the meta-analysis of trials using Psychological General Well-Being Index (PGWB) reported a statistically significant increase in the total score and the components of positive well-being and vitality compared to placebo treatment. However the clinical significance of an improvement of one to four points on the 110 point PGWB scale was unclear. Additionally the PBAC noted that two trials (Hoffman 2004 and Underwood 2003), which were excluded from the PGWB meta-analysis, reported that treatment with somatropin resulted in no significant change in QoL using a number of assessment tools including the PGWB, and that inclusion of these trials in the PGWB meta-analysis may have resulted in the difference in PGWB scores no longer reaching statistical significance. Importantly, the PBAC also noted that the two trials that assessed QoL using the QoL-AGHDA reported no significant effect of treatment with somatropin.

The PBAC noted the heterogeneity and small size of the trials. The PBAC further noted that the trials had limited follow up, and hence that long term effects of treatment with somatropin were uncertain.

The PBAC accepted the submission's claim that somatropin is inferior in terms of short-term safety to placebo. The PBAC considered that the long-term safety of somatropin is uncertain.

The PBAC noted that the clinical trial evidence presented in the submission was not translated to form the basis of the economic evaluation as the submission considered the patient populations in the trials were not applicable to the requested PBS patient population as: the entry criteria did not include patients impaired QoL at baseline; the trials generally used generic QoL instruments (not AGHD specific); and the trials typically had small patient populations. The submission analysed a subgroup of patients with impaired baseline QoL from the Pfizer International Metabolic Database (KIMS) for the economic evaluation. The PBAC noted that the KIMS database is an observational database which contains few untreated patients and hence considered that the KIMS data were non-comparative and likely to be highly selective of patients successfully treated with somatropin.

The PBAC considered there were significant uncertainties and potential sources of selection bias associated with the subgroup of patients from the KIMS database used in the economic evaluation. The PBAC noted that the subset of patients with a QoL-AGHDA of 15 or greater at baseline was chosen to match the requested PBS population, but it was unclear what the clinical reasons for the selection of this baseline score were.

The PBAC also noted that patients who did not have follow-up at each time 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 that the exclusion of patients without follow-up was a source of bias in favour of somatropin in that patients who continued treatment were the most likely to be responding to treatment as those with lack of efficacy or adverse effects were more likely to discontinue treatment. Further, patients who did not complete QoL questionnaires were likely to have poorer QOL than those who did.

The submission transformed QoL-AGHDA total scores from the KIMS sample of patients to EQ-5D index scores based on a published transformation algorithm (Koltowska-Haggstrom 2007), which was based on mapping of QoL-AGHDA to EQ-5D of a large general population sample and assumed 100 % correlation between these instruments. The PBAC considered this increased the uncertainty, noting that this approach may not capture important aspects of QoL associated with the requested PBS patient population, particularly as the requested PBS population were patients with a reasonably low quality of life on the QoL-AGHDA at baseline, and there were very few patients in the Koltowska-Haggstrom sample with QoL in this range.

The PBAC hence considered that the ICERs generated from the economic evaluation were highly uncertain.

The PBAC hence rejected the submission on the basis of uncertain clinical benefit and highly uncertain cost effectiveness.

The PBAC acknowledged and noted the consumer comments received in its consideration of somatropin.

The PBAC recommended amending the wording of the listing of somatropin to correctly reflect the current version of the Guidelines for the PBS Growth Hormone Program, noting that there are no longer separate guidelines for the availability of growth hormone for the treatment of Prader-Willi Syndrome.

The PBAC further recommended amending the wording of the listing of somatropin to remove the description of Genotropin branded products.

Recommendation:
Reject

13. 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.

14. Sponsor's Comment

Pfizer is disappointed with the PBAC's decision as there is a significant unmet clinical need for patients with severe adult growth hormone deficiency.