PUBLIC SUMMARY DOCUMENT
Product: Somatropin, powder for injection and diluent (cartridge), 5 mg per mL, 12 mg per mL (with preservative), powder for injection and diluent (single dose syringes) in strengths from 0.6 mg – 2 mg per 0.25 mL, Genotropin® and Genotropin MiniQuick®

Sponsor: Pfizer Australia Pty Ltd

Date of PBAC Consideration: March 2008

1. Purpose of Application

The application sought an extension to the Section 100 human Growth Hormone (hGH) program and the *"Guidelines for the Availability of human Growth Hormone (hGH) as a Pharmaceutical Benefit"* to allow treatment for the improvement of body composition and short stature associated with Prader-Willi Syndrome (PWS) in paediatric patients.

2. Background

The PBAC had previously considered several submissions seeking PBS availability of hGH in patients with PWS. Overall, the submissions were rejected due to the limitations around the evidence to support the extent of benefit and the resulting uncertain cost-effectiveness of the treatment. The PBAC also noted that a proportion of children with PWS could access hGH if meeting the growth related criteria of the Guidelines.

3. Registration Status

Genotropin 5 mg per mL, 12 mg per mL and Genotropin MiniQuick (all strengths) are registered with TGA and indicated for:

- treatment of 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;
- 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

Section 100: Human Growth Hormone Program

Improvement of body composition and treatment of short stature associated with Prader-Willi Syndrome in paediatric patients.

The sponsor also requested a revision of the current Growth Hormone Guidelines to include use of Genotropin for children with Prader-Willi Syndrome.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Prader-Willi Syndrome (PWS) is a complex, multi-system, genetic disorder characterised by neonatal hypotonia, developmental delay, short stature, behavioural abnormalities, childhood-onset obesity, hypothalamic hypogonadism, and characteristic appearance. The greatest morbidity and mortality in the syndrome is attributed to complications resulting from being overweight or obese, related to the central distribution of fat in the abdomen, chest and neck areas. In paediatric patients who have growth hormone deficiency due to PWS, treatment with Genotropin stimulates linear growth and normalises concentrations of IGF-1 (insulin-like growth factor-1) and produces improvements in body composition and lipid metabolism.

6. Comparator

The re-submission nominated placebo as the main comparator. This was accepted by the PBAC as appropriate.

7. Clinical Trials

The re-submission presented seven randomised comparative trials comparing somatropin and placebo, and one supportive randomised long-term case-control study comparing somatropin and placebo.

The studies as published at the time of the re-submission are presented in the table below.

Trial/First author	Protocol title	Publication citation
Randomised comparative trials		
Carrel 1999	Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome: A controlled study.	The Journal of pediatrics, 1999. 134(2): p. 215-21.
Festen 2007a	Adiponectin levels in prepubertal children with Prader-Willi syndrome before and during growth hormone therapy.	J-Clin-Endocrinol-Metab. 92(4): p. 1549-54.
Festen 2007b	Thyroid hormone levels in children with Prader-Willi syndrome before and during growth hormone treatment.	Clin Endocrinol. Oxford. 67(3):449-56.
Haqq 2003	Effects of growth hormone on pulmonary function, sleep quality, behavior, cognition, growth velocity, body composition, and resting energy expenditure in Prader-Willi syndrome.	The Journal of clinical endocrinology and metabolism, 2003. 88(5): p. 2206-12.
Hauffa 1997	One-year results of growth hormone treatment of short stature in Prader-Willi syndrome.	Acta paediatrica (Oslo Norway: 1992). Supplement, 1997. 423: p. 63-5.
Lindgren 1997	Effects of growth hormone treatment on growth and body composition in Prader-Willi syndrome: a preliminary report The Swedish National Growth Hormone Advisory Group.	Acta paediatrica (Oslo Norway : 1992). Supplement, 1997. 423: p. 60-2.
Whitman 2004*	Growth hormone improves body composition and motor development in infants with Prader-Willi syndrome after six months.	Journal of pediatric endocrinology & metabolism : JPEM, 2004. 17(4): p. 591-600.

Supportive study		
Angulo 2007	Final adult height in children with Prader-Willi syndrome with and without human growth hormone treatment.	American journal of medical genetics. Part A, 2007. 143(13): p. 1456-61.

* Trial in infant population only

8. Results of Trials

A meta-analysis was undertaken to combine the results of the studies, where appropriate, to give an overall view of the effect of hGH on patients regardless of their stature or age at entry. The key results from the meta-analysis are summarised in the table below.

Summary of results from the meta-analysis

Outcome	Population	WMD Somatropin vs. No Treatment
Height velocity	All trials	5.94 cm/year (95% CI: 5.05, 6.82).
	Excluding infants	5.93 cm/year (95% CI: 4.77, 7.09)
Height SDS	All trials	1.04 (95% CI: 0.58, 1.51)
% body fat	All trials	-9.58% (95% CI: –12.70%, –6.46%)
LBM	All trials	3.01 kg (95% CI: 1.24, 4.78)
	Excluding infants	4.0 kg (95% CI: 2.54, 5.46)
BMI	All trials	-2.21 (95% CI –3.14, -1.27)

Abbreviations: WMD= weighted mean difference; SDS= standard deviation score; LBM=lean body mass; BMI= body mass index.

Children treated with somatropin experienced significant improvements in height standard deviation score (SDS), percentage body fat, lean body mass and body mass index compared with untreated children.

All studies reported either a significant difference or trend towards significant difference favouring somatropin treatment over placebo.

The results for the outcome of respiratory function are summarised in the following tables.

Inspiratory muscle strength (cm/H_2O) at baseline and 1 year

Trial ID	hGH treatment			Untreated control		
	n/N (%)	Baseline Mean (SD)	Endpoint Mean (SD)	n/N (%)	Baseline Mean (SD)	Endpoint Mean (SD)
Carrel (1999)	35/35 (100)	45.8 (23.4)	55.7 (13.7) $p<0.01$[1]	19/19 (100)	44.8 (13.2)	40.4 (13.9)

[1]Paired t-test before and after GH therapy, compared with either baseline values of treated patients or 12 month values of untreated patients

Expiratory muscle strength (cm/H_2O) at baseline and 1 year

Trial ID	hGH treatment			Untreated control		
	n/N (%)	Baseline Mean (SD)	Endpoint Mean (SD)	n/N (%)	Baseline Mean (SD)	Endpoint Mean (SD)
Carrel (1999)	35/35 (100)	54.6 (23.8)	69.3 (20.8) $p<0.01$[1]	19/19 (100)	58.8 (22.1)	46.0 (13.3)

[1]Paired t-test before and after GH therapy, compared with either baseline values of treated patients or 12 month values of untreated patients

The results indicate that after 12 months therapy children receiving somatropin show significant improvements in both inspiratory and expiratory muscle strength compared with baseline values of treated patients, or end point values of untreated patients.

The PBAC noted that the prevalence of diabetes among PWS patients who have not received hGH intervention is significantly higher than among those who have been treated with hGH.

The re-submission presented a summary of the most recent Periodic Safety Update Report (PSUR) for somatropin. The key results are summarised below.

A total of 671 cases containing 1,120 events were included in the PSUR, with the most commonly reported adverse events being headache, scoliosis, neoplasm recurrence and incorrect dose administered. Events reported in ≥2% of cases are shown the table below.

Events reported in ≥2% of all cases (11 Aug 2004 – 10 Aug 2006)

Preferred term	Number of cases (%)
Headache	33 (4.9)
Condition aggravated	31 (4.6)
Scoliosis	31 (4.6)
Neoplasm recurrence	26 (3.9)
Incorrect dose administered	31 (3.1)
Pyrexia	19 (2.8)
Fatigue	18 (2.7)
Drug exposure during pregnancy	18 (2.7)
Drug administration error	16 (2.4)

The key finding of the PSUR was that "there were no major findings bearing on the established overall safety of somatropin".

9. Clinical Claim

The submission claimed that somatropin was therapeutically superior to the comparator, with higher toxicity. Based on the supporting data, the PBAC considered this description was reasonable.

10. Economic Analysis

A stepped modelled economic evaluation was presented. The model was in two parts. Part A modelled subjects from the age of six months to 17 years, and were treated with somatropin. All survivors at age 18 years were channelled into Part B of the model. Part B simulated the follow-up of subjects from age 18 years to a maximum of 50 years. Part B of the model did not directly apply any effects or costs of treatment with somatropin. The effects of treatment (from Part A) are mediated by the difference between the placebo and somatropin groups in the proportions of subject with and without diabetes at baseline in Part B. In other words, for patients aged ≥ 18 years, Part B of the model assumed that no additional mortality benefit was associated with somatropin beyond that already achieved in earlier life.

The economic evaluation produced an incremental cost per extra Quality-Adjusted Life-Year (QALY) gained between $45,000 and $75,000.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of patients per year to be less than 10,000 in Year 5 with an estimated financial cost per year to the PBS of less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended amending the listing of somatropin on the PBS under the Section 100 Human Growth Hormone Program 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.

The PBAC accepted that the administration of somatropin to PWS patients less than 18 years results in significant improvements in body composition and respiratory muscle strength and there appears to be a reduction in mortality, and in some patients there may also be a reduced prevalence of diabetes, both of which are clinically important benefits. The PBAC considered that use of somatropin in PWS be limited to patients up to 18 years of age as there is no data outside this age group.

The PBAC did not consider the rule of rescue applicable although acknowledging that patient numbers are small and as a result, the database is limited.

The PBAC considered that the incremental cost /extra QALY gained of between $45,000 and $75,000, although associated with some uncertainty, represents acceptable cost-effectiveness.

The PBAC requested the Growth Hormone Advisory Committee provide advice to the PBAC on the amendments required to the 'Guidelines for the Availability of Human Growth Hormone (hGH) as a Pharmaceutical Benefit' for the provision of growth hormone to patients up to the age of 18 years for the management of PWS.

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 Australia (the Sponsor) is delighted with the PBAC's decision to recommend the inclusion of Genotropin on the PBS for children with PWS. The sponsor believes the availability of this medicine provides a significant advance in the treatment paradigm for these children with PWS. The Sponsor appreciates the opportunity to work with the stakeholders to achieve this positive outcome for children with PWS and their families in Australia.