PUBLIC SUMMARY DOCUMENT

Product: Somatropin, powder for injection and diluent, 5 mg per mL, 12 mg per mL (with preservative), powder for injection and diluent (single dose syringes) in strengths from 0.8 mg – 2 mg per 0.25 mL, Genotropin® and Genotropin MiniQuick®

Sponsor: Pfizer Australia Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The resubmission sought an extension to the Section 100 human Growth Hormone (hGH) program *"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

At the December 2001 meeting, the PBAC rejected a minor submission from the then sponsor of the product, Pharmacia Australia Pty Ltd, requesting that the *"Guidelines for the availability of human Growth Hormone (hGH) as a Pharmaceutical Benefit"(the Guidelines)* be amended to reflect that Genotropin is approved for marketing for use in patients with PWS, on the basis that such patients are already able to receive Genotropin as a pharmaceutical benefit based on auxological criteria.

At the December 2002 meeting, the PBAC considered a submission which requested that *the Guidelines* be amended to reflect that Genotropin products are approved for marketing in paediatric patients with PWS and as such PWS should be listed for special eligibility in a new Section of the Guidelines. Although the PBAC was sympathetic to this request, the submission was rejected because the Committee is legally required to examine the cost-effectiveness of proposed drugs for the requested purposes (the sponsor is in the best position to provide this information). The PBAC requested that advice be sought from the Australian Paediatric Endocrine Group (APEG) on the appropriate management of this patient group.

The APEG submitted a paper entitled "Prader-Willi Syndrome – The Case for Growth Hormone Therapy in Affected Children and Adolescents" which was considered at the July 2004 PBAC meeting. The PBAC was concerned that, while the APEG considered that there are a number of benefits of hGH in PWS, the extent of benefit and cost-effectiveness of hGH remained unclear. The PBAC noted that there was a specific lack of information about the benefits of hGH in PWS patients who currently do not qualify for PBS-subsidised hGH treatment under the auxological criteria specified in *the Guidelines* compared with those who do qualify.

3. Registration Status

All strengths of Genotropin have TGA approval 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

The sponsor requested relevant changes to the current Growth Hormone Guidelines to allow Genotropin to be used Section 100: Human Growth Hormone Program: for children with Prader-Willi Syndrome.

See Recommendation and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy

Prader-Willi Syndrome (PWS) is a complex, multi-system, genetic disorder characterised by neonatal low muscle tension, developmental delay, short stature, behavioural abnormalities, childhood-onset obesity, lack of function of gonads (ovaries or testes), 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.

6. Comparator

The resubmission nominated placebo as the main comparator. The PBAC accepted this as appropriate.

7. Clinical Trials

The resubmission presented five randomised comparative trials comparing somatropin with placebo in children with PWS.

These studies had been published at the time of submission, as follows:

Trial/First author	Protocol title	Publication citation
Carrel A et al (1999)	Growth Hormone Improves Body Composition, Fat Utilisation, Physical Strength and Agility, and Growth in Prader-Willi Syndrome: A Controlled Study.	The Journal of Paediatrics, 1999; 134: 215-221
The above also reported as: Myers SE et al (1999), Acta	Physical Effects of Growth Hormone treatment in Children With Prader-Willi Syndrome.	Paediatrica Supplement 88: 433; 112-14

Trial/First author	Protocol title	Publication citation
Myers SE et al (2000),	Sustained Benefit After 2 years of Growth Hormone on Body Composition, Fat Utilization, Physical Strength and Agility, and Growth in Prader-Willi Syndrome.	The Journal of Paediatrics 137;42-9
Carrel AL et al (2001),	Sustained Benefit of Growth Hormone on Body Composition, Fat Utilization, Physical Strength and Agility, and Growth in Prader-Willi Syndrome are Dose-Dependent.	The Journal of Paediatric endocrinology & Metabolism 14;1097-1105.
Carrel AL et al	The Benefits of Long –Term GH Therapy in Prader-Willi Syndrome: A 4-Year Study.	Journal of Paediatric endocrinology & Metabolism 14;1097-1105
Haqq et al (2003)	Effects of Growth Hormone on Pulmonary Function, Sleep Quality, Behaviour, Cognition, Growth Velocity, Body Composition, and resting Energy Expenditure in Prader-Willi Syndrome.	The Journal of clinical Endocrinology & Metabolism, 2003; 88(5): 2206-2212
Whitman B et al (2004)	Growth Hormone Improves Body composition and Motor Development in Infants with Prader-Willi Syndrome After Six Months.	The Journal of Paediatric Endocrinology & Metabolism, 2004; 17: 599-600
Carrel A et al (2004)	Growth Hormone Improves Body Composition and Motor Development in Infants and Toddlers with Prader-Willi Syndrome.	The Journal of Paediatrics 145;744-9
Hauffa B et al (1997)	One Year results of Growth Hormone treatment of Short Stature in Prader-Willi Syndrome.	Acta Paediatrica Supplement, 1997; 423: 63-65
Lindgren A et al (1997)	Effects of Growth Hormone Treatment in Growth and Body Composition in Prader-Willi syndrome: a preliminary report.	Acta Paediatrica Supplement, 1997; 423: 60-62
The above also reported as: Lindgren et al (1998)	Growth Hormone Treatment of Children with Prader-Willi Syndrome Affects Linear Growth and Body Composition Favourably.	Acta Paediatrica 87:28-31
Lindgren et al (1999)	Five Years of Growth Hormone Treatment in Children with Prader-Willi Syndrome.	Acta Paediatrica Supplement 433:109-11

8. Results of Trials

The results of the trials showed that with somatropin therapy, there was a reduction in percent body fat of approximately 4-8% from baseline, compared to approximately 4% increase in placebo over 6-12 months. This resulted in a differential of a statistically significant reduction of about 4-9% in body fat in favour of hGH.

Of the results from the four trials measuring body mass index (BMI) over 6-12 months, only one trial showed a significant reduction, although a trend favouring somatropin was seen.

The results of the two trials measuring energy expenditure demonstrated that patients treated with somatropin experience an increase in their energy expenditure compared with placebo-treated patients, but did not reach statistical significance.

The results of the four trials examining linear growth over 6-12 months demonstrated that patients treated with somatropin experience a greater height velocity compared with patients treated with placebo.

For PBAC's comments on these results, *see Recommendation and Reasons.*

9. Clinical Claim

The resubmission claimed that treatment with growth hormone is more effective than the main comparator, but has more toxicity.

10. Economic Analysis

The resubmission presented a preliminary economic evaluation using a cost-effectiveness approach. The PBAC considered this to be valid. The only resource included was drug costs.

The resubmission estimated that the trial-based incremental cost per extra percent reduction in body fat would be < $15,000.

The resubmission did not present a modelled economic evaluation. The PBAC considered that this was inappropriate.

For PBAC's comments, *see Recommendation and Reasons.*

11. Estimated PBS Usage and Financial Implications

The resubmission estimated that in Year 4 of listing, the likely number of patients would be < 10,000 and the financial cost per year to the PBS would be < $10 million.

12. Recommendation and Reasons

The PBAC considered that of all the outcome measures presented in the submission, the percent body fat reduction was the most convincing because they reached statistical significance. The question remained however, as to how this reduction could be extrapolated to outcome measures which are more patient relevant. Furthermore, the limited data presented seemed to indicate that any benefit may be removed on the cessation of somatropin (Hoybye (2005)). The PBAC noted that data presented, relating to changes in BMI and energy expenditure were not statistically significant, but did show a trend in favour of somatotropin. However, the studies were small in number and the power is likely to be inadequate.

The PBAC noted the estimated cost per patient per year of treatment to be in the range $15,000 - $45,000. This estimate was taken from the Pfizer International Growth database (KIGS) and equates to a mean dose of 0.22 mg per kg per week in children with a mean age of 8.39 years. The PBAC noted that this dose is less than that recommended in the product information (0.245 – 0.35 mg per kg per week) and less than used in the trials published by Carrel and Haqq where doses were 30% higher. The incremental cost per extra percentage reduction in body fat over 12 months estimated at $2609 was based on this dose of 0.22 mg

per kg per week. If the dose used in practice was 30% higher, this value would increase in proportion.

The PBAC considered that in the absence of any modelled analysis it is impossible to translate the trial based incremental cost into a cost per relevant health outcome. Furthermore, whilst it was acknowledged that a reduction in body fat in these patients is apparent with somatotropin, in view of the lack of evidence that any reduction is likely to be continued after cessation of therapy at 18 years, and what impact that has on cardiovascular risk factors and the reduction in diabetes, its cost effectiveness is highly uncertain. The PBAC also noted that there is no evidence presented in the submission on whether the behavioural problems associated with PWS are reduced with somatotropin.

The PBAC concluded that the submission's only justification for the substantial cost of this drug is the reduction in body fat from 45.8% with placebo to 38.4% with somatropin. The PBAC noted that the submission stated that this treatment effect will be maintained in relative terms in the longer term, and the ratio will improve if the control group worsens over time. The PBAC considered that while this is possible, there is no evidence to support this claim.

The PBAC also noted concern regarding the toxicity of somatropin in PWS patients and that this has been the subject of extensive correspondence between the sponsor and the TGA. The question as to whether somatropin is adequately safe in the long-term in the PWS population remains open. It was noted that under the current registration that somatropin is contraindicated in extremely obese patients with PWS.

In regard to any restriction or condition of PBS subsidy, the PBAC considered that eligibility for initiation of treatment should be based on genetic testing for PWS as all trial patients were genetically diagnosed and this is also included in the product information. Any continuation criteria should be based on achieving a certain percentage change in body fat. In regard to age limitations for initiation and cessation of treatment, the PBAC agreed that, given the registered indication allowed for treatment of paediatric patients only, treatment should cease at the age of 18 years, however acknowledged that this may impact on long term benefit of the drug. The PBAC noted that during the pre-PBAC consultation process, the sponsor was amenable to these conditions for listing. However, the issue of any limitation on the age of initiating treatment remained unresolved, and should be considered in any further resubmission.

Overall, whilst the PBAC was sympathetic to this small patient group and acknowledged that some patients with PWS were receiving PBS subsidy for somatropin based on auxological criteria under the current Growth Hormone Program, it rejected the submission as the long-term benefit of treatment is highly uncertain resulting in uncertain cost-effectiveness.

Any resubmission should include evidence relating to benefit on childhood development into adult life as well as benefit in regard to family and social functioning while on therapy. A modelled economic evaluation, to demonstrate value for money in terms of patient relevant outcomes should also be included.

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 intends to investigate the possibility of developing a model for a re-submission to PBAC.