Submission to Pharmac PTAC Committee

Proposed Amendment to the Special Authority Criteria SA1451

Somatropin Treatment for Prader-Willi Syndrome

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Submitted by the
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PWS NEW ZEALAND

SUPPORTING PEOPLE WITH PRADER-WILLI SYNDROME AND THEIR FAMILIES

Somatropin therapy for adolescents and adults with Prader-Willi syndrome

The Prader-Willi Syndrome Association (PWSANZ) were relieved that the PTAC recommended Somatropin treatment for children with Prader-Willi syndome (PWS) be funded from 6 months of age with no requirement to prove slow growth velocity.

Internationally, growth hormone treatment is standard of care for PWS and there was no clinical reason to delay or deny treatment based on age or growth velocity. The financial burden on several families who were self-funding their own growth hormone treatment has been lifted.

We were disappointed that the PTAC declined funding to at least 18 years of age and instead chose to end treatment based on skeletal maturity.

We have reviewed the minutes of the last PTAC meeting and we are grateful to have the opportunity to respond to the statements and recommendations made and to provide further points and new evidence.

Discussion of PTAC minutes

We would like to respond to the definition of PWS given in the minutes.

1. ***"The Committee noted that PWS is a rare genetic disorder affecting three to four new patients per year in New Zealand and is characterised by severe muscular hypotonia in the neonatal period resulting in feeding difficulties, mild to moderate intellectual disability, compulsivity, irritability, aggression, short stature, sleep apnoea and resulting cardio-respiratory problems, and eating disorders that include food cravings with extreme food-seeking behaviours that can lead to obesity."***

We realise the minutes are a summary of the points discussed but we would like to point out that this description omits some of the key characteristics of the syndrome which are thought to be related to hypothalamic dysfunction:

> hypogonadism, growth hormone deficiency, central hypothyroidism, central adrenal insufficiency, and an abnormal body composition.
>
> Hypotonia is ongoing: "People with PWS have a high body fat mass percentage(FM%) and a low lean body mass(LBM),even in the presence of a normal BMI." (Kuppens, et al., 2016)

2. ***"The Committee considered ….that environmental factors, such as control of appetite by carers, are likely to have the largest impact on body composition changes".***

We would like the committee to consider the example of type two diabetes where environmental factors like dietary management and exercise can play a part in ameliorating the disease. This has not precluded pharmacological treatments being approved and funded by Pharmac for type two diabetes.

Research shows that while calorific management might have an impact on weight, it does not improve body composition, i.e. increase the proportion of lean body mass as occurs during treatment with growth hormone.

We include the following picture from Dr Jennifer Miller's clinic in Florida to illustrate the impact of growth hormone treatment on body composition in PWS and note these effects were achieved when dietary and exercise interventions remained the same.

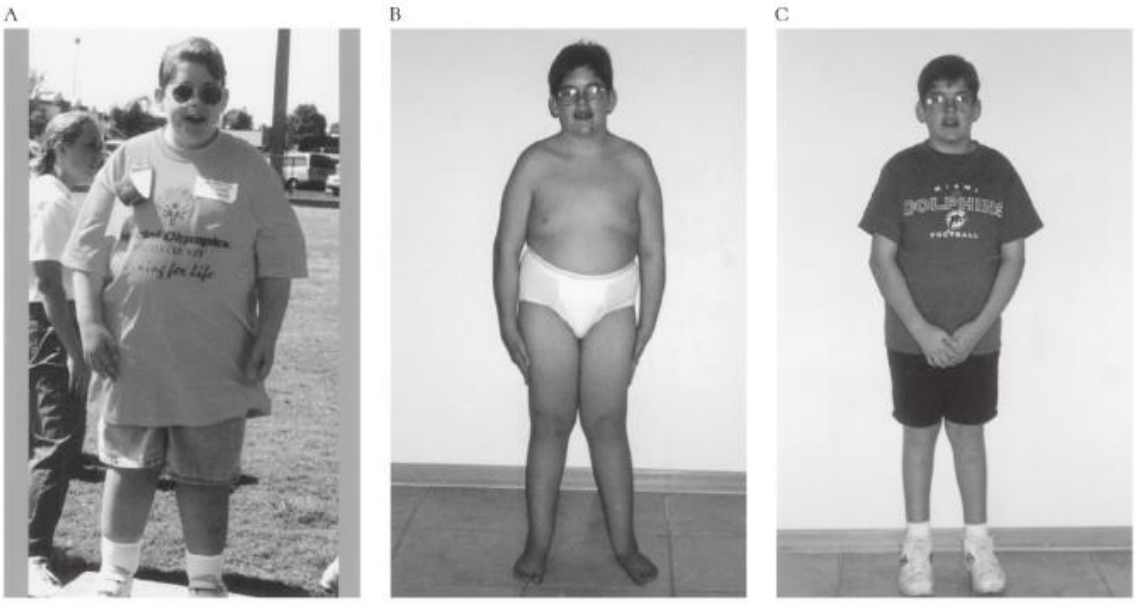

Figure 16–1. An adolescent male with Prader-Willi syndrome receiving growth hormone (GH) therapy at 0.033 mg/kg/day. A. Subject at 14 years of age, after 2 months of therapy. B. Subject after 9 months of therapy. C. Subject at 15 years of age, after 13 months of therapy. Notice the dramatic reduction of obesity in the waist, limbs, and face. The caloric restriction and exercise program that was in place before initiation of GH therapy was continued during the GH therapy. (Courtesy of University of Florida Health Science Center, Gainesville, Florida. Used with permission.)

3. ***"The Committee considered that from the currently available published evidence it was unclear what benefit, if any, somatropin treatment provided for adult and adolescent patients with PWS. The Committee also considered it was uncertain if any long-term clinically meaningful benefit would be derived from somatropin treatment in this patient population."***

Like people with non syndromic growth hormone deficiency (GHD), adults and adolescents with PWS have reduced muscle mass, muscle strength and bone mineral density, decreased heart geometry, increased cardiovascular risk profile, fatigue and without growth hormone treatment, can experience fatigue and a reduction in their quality of life.

In addition to this, people with PWS also have to contend with intellectual disability, hyperphagia, and behavioural issues which can all further impact their quality of life.

We believe that published research does show benefits for adults and adolescents with PWS and we would appreciate some more guidance from the PTAC regarding why they believe this is not the case.

The benefits of Growth Hormone therapy after attainment of adult height

Today there are numerous PWS studies which show the significant benefits of growth hormone treatment after the attainment of final height, in particular the improvements to body composition and exercise capacity. Some studies have also examined and noted other benefits in the areas of cognition, behaviour, mental health and quality of life.

It makes sense that the physical benefits would also impact on other areas of adult life, such as quality of life being improved by an increase in energy and exercise capacity which would allow an individual to be more actively involved in their community or place of work.

We listed over 20 papers regarding the benefit of GH treatment in adults and adolescents with PWS in our December 2015 submission which was supplied to the PTAC in September 2016.

We would like to discuss the most recently published study to investigate the effects of growth hormone versus placebo on body composition in young adults with PWS who were GH-treated for many years during childhood and had attained adult height. It is a 2-year, randomized, double-blind, placebo-controlled cross-over study in 27 young adults with PWS by Kuppens et al, 2016.

The results provided a clear, convincing case for maintaining the improved body composition with growth hormone treatment: during placebo, FM increased (relative change +21.5%, $p<0.001$). Compared to placebo, GH treatment resulted in lower FM (-2.9 kg, $p=0.004$) and higher LBM (+1.5 kg, $p=0.005$), representing relative changes of -17.3% FM and +3.5% LBM. Both $FM\%_{limb}$ and $FM\%_{trunk}$ were lower during growth hormone versus placebo (relative change +17.3% and +15.6%, $p<0.001$ and $p=0.007$, respectively). No growth hormone-related adverse events occurred. We include this paper as an attachment to this submission.

The recent paper by Dykens et al, 2016, found that similar to other groups of patients with growth hormone deficiencies, growth hormone treatment has beneficial effects on the cognitive and everyday adaptive functioning of children and youth with PWS. We include a letter from Drs Dykens and Roof outlining their current research and supporting our request for adolescents and adults to receive growth hormone treatment.

The review published in 2016 by Crino et al provides a summary of research to date and states:

"it has been demonstrated that GH replacement therapy is able to reduce fat mass and to increase fat-free mass in PWS adults, including patients in the transition phase. An increase of 19% in exercise capacity, evaluated using treadmill exercise testing, was reported in twelve PWS adults (including five transition patients) after 1 year of GH therapy. Long-term GH treatment in 15 PWS adults (seven in the transition phase) ameliorated body composition, muscle size, and quality, and increased muscle strength and exercise tolerance .Improvement in mental speed and flexibility and motor performance tests during GH administration was detected in 19 PWS individuals with a median age of 25 years, with a rapid deterioration in physical and social status as well as overall functioning after GH therapy withdrawal. Moreover, it has been reported that cessation of GH therapy in young PWS patients worsened BMI, with a tendency toward increases in visceral adipose tissue" (Crinò, Fintini, S, Carducci, & Grugni, 2016).

We include this paper as an attachment to this submission.

Growth Hormone effects on quality of life

In 2015 Bakker et al published a study which had measured health related quality of life in a randomized controlled GH trial including 26 PWS children and during an 11-year longitudinal GH study in 76 children, and found that growth hormone-treated children reported an increase in HRQOL in the physical and social subdomains and the DUXPW (a PWS specific questionnaire) compared to untreated children. They concluded that PWS children rated HRQOL equally to or better than healthy and obese children. HRQOL increased during growth hormone treatment, in contrast to HRQOL of untreated children. This effect was sustained during long-term growth hormone treatment. (Bakker, Siemensma, van Rijn, Festen, & Hokken-Koelega, 2015)

Previous studies had also noted the growth hormone effects on overall functioning in PWS. As severe GHD of other aetiologies had been shown to affect mood and quality of life negatively and growth hormone replacement brings about an improvement, Hoybye et al conducted a pilot study in 2005 to examine the cognitive, emotional, physical and social parameters in PWS adults at baseline, during and after growth hormone treatment. They randomized 19 PWS patients with a median age of 25 to 6 months of treatment with either GH [1.6 IU/day (0.53 mg/day)] or placebo, followed by 12 months of active growth hormone treatment. Treatment was then stopped, and the patients were followed for an additional period of 6 months. Improvement in mental speed and flexibility and motor performance tests during growth hormone administration was detected in all PWS individuals with a rapid deterioration in physical and social status as well as overall functioning after growth hormone therapy withdrawal. (Hoybye, Thoren, & Bohm, 2005)

In 2007, Bertella et al specifically assessed the long-term effect of growth hormone treatment on the psychological well-being and Quality of Life (QoL) in an adult PWS group. The 13 PWS participants were administered the 36-Items Short Form Health Survey (SF-36) and the Psychological General Well-Being Index (PGWBI), for the assessment of QoL and psychological well-being, at the beginning of growth hormone treatment, and at following intervals of 6, 12 and 24 months. Modified versions of the same questionnaires were given to the parents. Significant improvement with respect to the baseline was found, on both scales, in the evaluation of both physical and psychological well-being. They concluded that the amelioration of QoL and psychological status is sustained in patients who continue growth hormone treatment. (Bertella, et al., 2007)

A more recent study by Butler et al in 2013 reported on the effects of growth hormone treatment on adults with PWS during one year of treatment and after one year of cessation of treatment. Quality of life assessments (i.e., SF-36) were recorded in relationship to repeated body composition, blood chemistry and hormone levels, dietary records and strength indices in the selected PWS adults at baseline, after 12 months of growth hormone treatment and at 24 months while off growth hormone treatment for 12 months. The quality of life instruments showed improvement with higher scores recorded for 4 of the 8 variables tested between baseline and at 12 or 24 months implying improvement during growth hormone treatment for emotional and physical health, energy and social sensation. Several beneficial effects diminished to near baseline after cessation of growth hormone treatment for 12 months supporting the continuation of treatment in PWS into adulthood. (Butler, et al., 2013)

GHD and Growth Hormone treatment in PWS

The current special authority for growth hormone treatment for adults and adolescents requires applicants to prove their GHD status and demonstrate a reduced quality of life. In figures released from Pharmac we note that as many as 200 adults receive growth hormone treatment based on the entry criteria discussed with renewal also based on quality of life parameters.

We note that the data about the prevalence of GHD in PWS children is not unequivocal, ranging from 40% to 100% yet children with PWS receive funded growth hormone treatment based on theirresponse to the treatment.

"..the clinical picture of PWS subjects is similar to those observed in individuals with nonsyndromic GHD. In this context, however, few data about GH secretion throughout the transitional period in PWS are available. With GHRH plus arginine as provocative agents, 33% of a group of 24 PWS patients evaluated using BMI-specific cutoff values during the transition phase met diagnostic criteria for severe GHD. In another study, two of seven PWS subjects (28%) had GH peak levels after GHRH plus arginine test <9 µg/L. More recently, GHD was demonstrated in five of twelve PWS subjects aged 18 to 25 years."

"It is noteworthy that GH administration leads to a significant improvement of IGF-I levels, lean body mass, cardiovascular outcomes, strength development, and exercise capacity both in PWS adults with and without GHD. This observation could be of interest in the strategic perspective of the use of GH therapy in PWS adults, since the beneficial effects deriving from GH administration seem to be independent from a concomitant diagnosis of GHD." (Grugni, Sartorio, Antonino, & Crinò, 2016)

Data from Kuppens et al 2016 supports these statements finding that:

After the 2-year study, twenty four (88.9%) young adults underwent anarginine-GHRHtest. Only3 (12.5%) had a GH peak below the BMI-dependent cut-off (19). There was no significant influence of the GH peak on the effects of GH vs placebo treatment on FM%, FM or LBM."

Summary

A 2015 study published using data from the PWSAUSA database reported a total of 486 deaths (263 males, 217 females, 6 unknown) between 1973 and 2015 with mean age of 29.5 ± 16 years (2 months–67 years); 70% occurred in adulthood. Respiratory failure was the most common cause, accounting for 31% of all deaths.

PWS patients often die at an early age because of complications usually linked to obesity, which include respiratory problems, heart disease, and type 2 diabetes mellitus. (Crinò, Fintini, S, Carducci, & Grugni, 2016)

We believe that research shows that growth hormone treatment in adults and adolescents with PWS improves body composition and exercise tolerance, which lessens the likelihood of them developing morbid obesity and associated co-morbidities.

The recently published growth charts for growth hormone treated children and adolescents with PWS shows that no pubertal growth spurt is seen, and the 50th percentile for height is not reached until 18 years of age. We suggest that the current renewal criteria which includes the requirement for 50% height velocity and greater than 2cm per year is not appropriate for teenagers with PWS. (Butler, 2016)

What we hear from families is that growth velocity is variable in the teenage years and under the present criteria can cause treatment to be suspended and then reinstated after a period of no treatment slowing growth enough to qualify again. This is extremely stressful. We note that dietary and behavioural management take a huge toll on families impacted by PWS, and that the teenage years are particularly difficult. A statement from one of these families is attached to this submission.

As mentioned in our previous Dec 2015 submission, there are detrimental effects of cessation of treatment and the transition years are not an ideal time for these to occur. A new study by Bohm et al (previously not referenced) reported children with PWS showed a marked exacerbation of behaviour problems when growth hormone treatment was abruptly ceased. (Böhm, Ritzén, & Lindgren, 2015)

We propose amending the current criteria to remove the requirement for height velocity and 2cm per year of growth, and extend treatment to a chronological age of at least18 years.

We also propose the development of a separate special authority for adults with PWS based on a severe decline in the quality of life once growth hormone treatment has ceased.

PWS is a rare condition. Studies will not be as large as the PTAC may be used to assessing. But we strongly contest the view that there is no benefit derived from growth hormone treatment in this population.

Attachments

Kuppens et al 2016 "Beneficial effects of growth hormone in young adults with Prader-Willi syndrome: a 2-year cross-over trial."

Dykens and Roof letter of support and discussion of their recent research "Cognitive and adaptive advantages of growth hormone treatment in children with Prader-Willi syndrome"

Crinò, et al 2016 "Prader–Willi syndrome: clinical problems in transition from paediatric to adult care"

Growth Charts for Prader-Willi Syndrome During Growth Hormone Treatment

Supporting statements from patient families

References

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