Submission to Pharmac PTAC Committee

Proposed Amendment to the Special Authority Criteria SA1451

Somatropin Treatment for Prader-Willi Syndrome

December 2015

Submitted by the
Prader-Willi Syndrome Association (NZ) Inc.
PO Box 258 Silverdale 0944, North Auckland
Phone: +64 3 546 5405 | 027 673 1007
Email: ceo@pws.org.nz
www.pws.org.nz

PWS NEW ZEALAND

SUPPORTING PEOPLE WITH PRADER-WILLI SYNDROME AND THEIR FAMILIES

Proposal to widen the access to Somatropin therapy for Prader-Willi syndrome

Pharmac proposed updating the Special Authority Criteria for somatropin therapy for PWS, SA1451, as part of their Proposal for Various Pharmaceuticals published 20th May 2015.

The update involved removing the height velocity requirement of <25 percentile and the requirement to collect six months of growth data from 12 months of age. These changes acknowledge the primary benefit of growth hormone (GH) treatment in this population is improved body composition, and that there are benefits to starting growth hormone treatment as early as possible, once safety criteria are met.

The PWSA(NZ) made a submission supporting the update and proposing the growth velocity measurements were removed from the renewal criteria for the same reasons, and that treatment be continued until at least 18 years of age.

Several issues were raised in submissions which Pharmac felt warranted further review by the PTAC committee, namely: the benefits and safety of growth hormone treatment in infancy, what the renewal criteria should be, and the benefits of continuing treatment until at least eighteen years of age.

The PWSA(NZ) obtained a copy of all submissions through an OIA request and we were pleased to note the support for the changes proposed. We will address the issues raised in this submission.

We propose the Special Authority for Subsidy SA1451 for Prader-Willi syndrome be amended to the following:

Initial application — (Prader-Willi syndrome)
Applications only from a paediatric endocrinologist or endocrinologist. Approvals valid for 6 months for applications meeting the following criteria:
1 The patient has a diagnosis of Prader-Willi syndrome that has been confirmed by genetic testing or clinical scoring criteria.
2 The patient is under eighteen years of age. *
3 Sleep studies or overnight oximetry have been performed and there is no obstructive sleep disorder requiring treatment, or if an obstructive sleep disorder is found, it has been adequately treated under the care of a paediatric respiratory physician and/or ENT surgeon.
4 There is no evidence of type II diabetes or severe obesity.

Renewal application - (Prader-Willi syndrome)
Applications only from a paediatrician or endocrinologist. Approvals valid for 12 months for applications meeting the following criteria:
1 The patient has had a follow up sleep study or overnight oximetry 3-6 months after GH treatment began and there is no obstructive sleep disorder requiring treatment, or if an obstructive sleep disorder is found, it has been adequately treated under the care of a paediatric respiratory physician and/or ENT surgeon.
2 The patient is less than 18 years of age. *
3 The patient's IGF-1 level has been tested in the last 12 months and is not more than 2 standard deviations above the age matched mean.
4 No malignancy has developed after growth hormone therapy was commenced.
5 The patient has not developed type II diabetes or uncontrolled obesity as defined by BMI that has increased by ≥ 0.5 standard deviations in the preceding 12 months.

* An age beyond 18 years preferable, ideally continuing through adulthood for as long as the benefits outweigh the risks. (Refer to pages 9-11)

Introduction - The purpose of growth hormone treatment for children with Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a rare and complex genetic disorder that affects approximately 1 in 16,000 people.[1] It is a lifelong condition which can be life threatening.

PWS is characterized by short stature, abnormal body composition, hypotonia, developmental delay, cognitive disabilities, challenging behaviour, poor feeding in infancy, and hypothalamic dysfunction causing hyperphagia (excessive appetite) and obesity. PWS is caused by the lack of expression of paternally inherited genes on chromosome 15. [2,3]

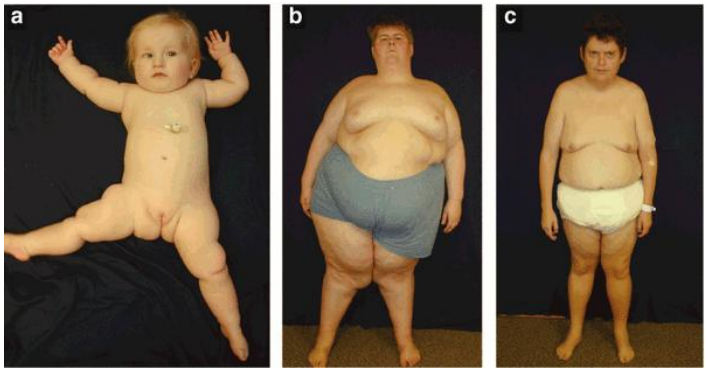

Figure 1: Abnormal body composition in PWS [3]
*An 8-month-old female with hypotonia, hypogonadism, and need for assisted feeding. (**b**) A 19-year-old male with inadequate dietary control showing fat distributed primarily in abdomen, hips, and thighs typical for PWS. (**c**) A 34-year-old man with good dietary control living in a specialized PWS group home.*

Individuals who have PWS require fewer calories than an unaffected person to maintain a healthy weight. This is due to their abnormal body composition which has less lean mass, particularly muscle mass, causing a low resting energy expenditure and a decreased capacity to exercise. [2] There is no effective treatment for the excessive appetite that develops in early childhood. Hoarding, foraging and stealing food are common. PWS is recognised as the most common genetic cause of life threatening obesity.

Growth hormone (GH) was approved to treat PWS in the USA in 2000, and Europe in 2001. Prior to GH treatment, even children with good dietary control exhibited the typically abnormal body composition shown in Figure 2 below. The new generation of GH treated PWS children look considerably different.

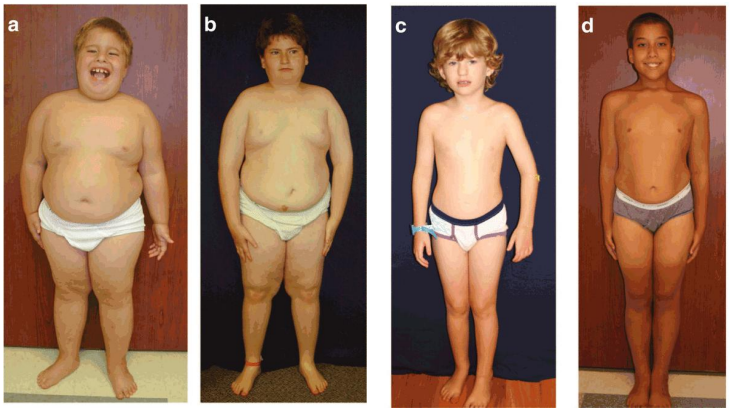

Figure 2: Improved body composition with GH treatment [3]
(a and b) Seven- and 13-year-old children, respectively, not receiving growth hormone treatment. (c and d) Seven- and 13-year-old children, respectively, who have received growth hormone treatment.

For children with Prader-Willi syndrome, the primary benefit of growth hormone treatment is not an improvement in linear height, but the significant changes in body composition that treatment provides. The most important reason for treatment is to create optimised body composition. [4]

Growth Hormone treatment has been used internationally for children with Prader-Willi syndrome for well over a decade, and numerous longitudinal studies have been able to examine the long-term benefits of treatment, and have reported that GH has positive long-term effects on body-composition. [4,5,6,7]

In response to a question raised in the submissions regarding the indications for GH treatment, we note that Medsafe New Zealand first approved GH (somatropin) in 1989 with the indications:

"Prader-Willi syndrome, for improvement of growth and body composition" for children, and "Prader-Willi syndrome, for improvement of body composition" for adults.

These same indications can be seen in the various different brands of approved somatropin since then, including the current brand Omnitrope.

In 2013, a Dutch study by Bakker et al reported findings after following 60 children for eight years, taking annual body composition measurements via DEXA scanning. They concluded:

> "GH treatment is a potent force for counteracting the clinical course of obesity in children with PWS." [4]

International best practice does not support the restriction of treatment to only those with low growth velocity.

In 2012, a panel of 43 international experts conducted a systematic review of the clinical evidence and published the International Consensus Guidelines for GH treatment in PWS that recommended:

> "*GH treatment should be considered for patients with genetically confirmed PWS…*"

And that

> "*Exclusion criteria should include severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnoea, active cancer, or psychosis.*"

And that

> "*Treatment should be continued for as long as demonstrated benefits outweigh the risks*" [8]

The requirement for slow growth velocity was removed from the Australian GH treatment programme for Prader-Willi syndrome in 2009, with treatment continuing until 18 years of age.

Recently published research on the updated Australian GH program compares the response to GH treatment in those treated on the basis of a genetic diagnosis of PWS to those with short stature as evidence of GH deficiency. Both cohorts showed improved height and lowering of BMI relative to PWS standards, supporting the efficacy of treatment based on genetic diagnosis alone. [9]

Unmet Health Needs

In New Zealand, GH therapy for children with PWS was first funded in 2005, when a small percentage of children with Prader-Willi syndrome were eligible to receive growth hormone treatment, provided their height was below the 3rd percentile. This meant, in practice, that children from "shorter" parents were more likely to qualify for the treatment than children from "taller" parents.

A further review of the eligibility criteria was completed in 2009. This 2009 review was a positive move forward, allowing more children to access treatment, but the criteria remain more restrictive than those introduced in the USA and Europe in 2000/2001, and are not in line with the new International Consensus Guidelines formulated by 43 international experts in 2012. [8]

Since 2009, the science and clinical practice regarding the use of GH in PWS have advanced considerably, particularly in relation to treatment during infancy and throughout adulthood.

Figures obtained from Pharmac show there were 31 children with Prader-Willi syndrome receiving GH treatment in the 2013/14 financial year. The PWSA (NZ) is aware of 4 families with children under 1 year of age who have, over the last three years, self-funded GH treatment on the advice of their endocrinologist, when Government funded treatment was not available to them. As their child grows and the cost of treatment increases significantly, these families must choose to cease treatment for a period until their child's growth has slowed sufficiently for the child to qualify for funded GH, or continue to bear the mounting financial burden themselves. Limiting treatment to only those families that can afford to self-fund GH treatment for their infants is extremely unfair.

There have been at least ten applications for GH for PWS declined since 2009. Several of these were appeals against the exit from treatment due to slow growth. These children may be unfairly discriminated against for following familial growth patterns. In addition, it has been shown that GH deficiency in PWS increases with age, making judgements regarding slow growth problematic.[36] There have been at least four children who were initially denied treatment, but who went on to qualify for funded treatment as their growth slowed in subsequent years, thus missing out on valuable years of treatment. These children are also unfairly discriminated against for sudden growth which can occur whilst entering phase 2a of the unique nutritional phases described in Prader-Willi syndrome. [20]

The current criteria do not acknowledge that for individuals with PWS

- There are clear benefits to starting growth hormone therapy in infancy, and well prior to 18 months of age
- The primary benefit of GH treatment is improved body composition, not an improvement in linear height
- International best practice does not support the restriction of treatment to only those with a reduced growth velocity of below the 25th percentile.
- Growth velocity outcomes are not an appropriate measure of evaluating treatment in this patient group
- Growth hormone treatment has benefits in adulthood

The current access criteria have created a subset of the PWS population with significant unmet health needs. We ask that they are urgently updated to reflect the purpose of growth hormone treatment for PWS, which is to improve body composition, not height.

The benefits of growth hormone treatment in infancy

1. **Early GH treatment improves body composition and motor development**

Controlled studies have shown that GH treatment during childhood in patients with PWS normalizes height, increases lean body mass, and improves motor development and activity level. [10,11,12,13,14]

Research has shown that the earlier treatment is started, the more benefit is derived by the patient. It has been shown that those treated with GH before age one had decreased fat mass, lower BMI, and higher resting energy expenditure as they age, compared to those treated after age one, indicating that early treatment with GH may help prevent or ameliorate the obesity associated with PWS. [4,15,16,17,18]

Studies have shown that infants with PWS have a greater improvement in their motor skills when treated with GH prior to 18 months of age.[19] This confirms the anecdotal reports from families who have begun GH in infancy – their child "wakes up", is less floppy, more interactive and generally more robust.

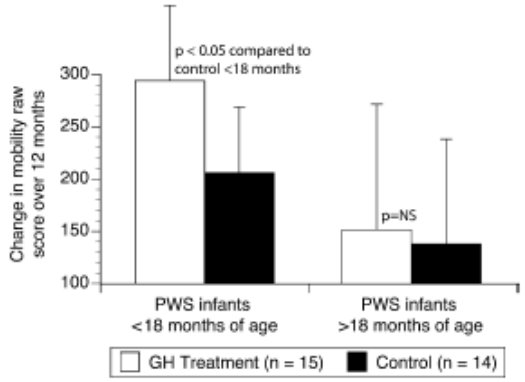

Figure 5: GH treatment reduces developmental delay when begun prior to 18 months of age. [19]

In 2010, Carrell and the team from the University of Wisconsin published the results of their six year study comparing two groups of age matched children. One group was treated with GH for six years. The second group, from a historic study, had received no treatment with GH. (Given that GH therapy is now internationally acknowledged as the standard of care for PWS, a long term randomized, controlled trial would be very difficult and possibly unethical.)

By performing identical tests of body composition, physical function, and lipid and carbohydrate metabolism in two groups of age and gender matched children with PWS, one of which was treated with GH early in life, this study has provided the strongest evidence to date that the positive effects of GH therapy early in life justify the initiation of treatment in infancy. [17]

The "early treatment" cohort consisted of 21 infants with PWS aged between 4–20 months when GH therapy was started.

> "When compared with school-aged children with PWS who had not been treated with GH, the early-in-life GH treatment children showed, on average:
>
> 1) 8.5% (absolute) reduction in body fat (19% relative reduction);
>
> 2) nearly a doubling in broad jump and sit-up performance;
>
> 3) 14 mg/dl higher HDL cholesterol levels and 31 mg/dl lower LDL cholesterol levels; and
>
> 4) height increased by 16 cm." [17]

These results validate the anecdotal reports from parents of improved ability and engagement in physical activities as a result of GH treatment. This in turn has an effect on weight management, quality of life and a child's ability to participate fully in their environment, particularly in the crucial learning years of childhood.

2. **GH treatment in infancy shortens the failure to thrive stage**

Infants with Prader-Willi syndrome have a weak suck and most require nasogastric or gastrostomy tube feeding for the first 3-6 months. Most infants also exhibit failure to thrive. This is an extremely stressful time for families, with their fragile baby often requiring many hospital or home visits from the paediatric outreach team. Growth hormone therapy has been shown to shorten this failure to thrive stage.

Families of children and adults with PWS have been enrolled in a natural history study conducted at the University of Florida over the last ten years which studied growth, metabolic parameters and behaviour allowing them to document the nutritional phases of PWS.

Phases	Median ages	Clinical characteristics
0	Prenatal to birth	Decreased fetal movements and lower birth weight than sibs
1a	0–9 months	Hypotonia with difficulty feeding and decreased appetite
1b	9–25 months	Improved feeding and appetite and growing appropriately
2a	2.1–4.5 years	Weight increasing without appetite increase or excess calories
2b	4.5–8 years	Increased appetite and calories, but can feel full
3	8 years to adulthood	Hyperphagic, rarely feels full
4	Adulthood	Appetite is no longer insatiable

Modified from *Am J Med Genet A*.[3]

Figure 6: Nutritional Phases of PWS [20]

The study looked at whether starting GH in infancy, as opposed to starting GH later in childhood, made any difference in the timing or natural history of these nutritional phases. Starting GH in infancy accelerated the pace of phase 1a ($P = 0.039$) ("hypotonia with difficulty feeding"), thus allowing the infants to enter phase 1b ("improved feeding and appetite and growing appropriately") earlier.[20]

3. GH improves cognitive development

It has been shown that GH therapy accelerates the acquisition of motor skills in infants with PWS, allowing them to interact with their environment which positively influences cognitive development at this critical age. [6, 17,19]

Several studies have shown that early treatment with growth hormone can improve psychomotor development, cognitive scores and language development. [14, 18]

A study published in 2012 found that during a two year randomized controlled trial of fifty children with PWS, cognitive function remained similar compared to baseline in GH-treated children, but declined in untreated controls. The research team went on to complete a longitudinal study to compare benefits when treatment time was extended. This showed significant improvement in abstract reasoning and visuospatial skills during four years of GH treatment. Children with a greater deficit had more benefit from GH treatment. [21]

The benefits of continuing growth hormone treatment until at least 18 years of age

Growth hormone treatment for children with Prader-Willi syndrome is currently withdrawn when the child attains a bone age of > 14 years (females) or > 16 years (males). It is not uncommon for children treated with growth hormone from early childhood to have an advanced bone age, meaning that in practice, the child's chronological age will be less than their bone age, so treatment may be withdrawn when a female is younger than 14 or a male younger than 16.

While we believe that GH treatment should in fact continue through adulthood for patients with Prader-Willi syndrome (and will, in due course, make a submission to Pharmac requesting this), as a first step in this process we request an amendment to the current renewal criteria so that treatment continues until a patient attains the age of at least18 years. There are a number of reasons for this, including:

1. The physical benefits of continuing growth hormone treatment

A recently published study concluded that GH treatment in childhood and adolescence is associated with significantly decreased body mass index and improved body composition and metabolic status in adults with PWS at several years after discontinuing treatment. [22]
These prolonged benefits of treatment would be best continued into early adulthood – an unsettled time of transition and change.

2. The detrimental effects of cessation of treatment

Cessation of growth hormone treatment brings its own set of challenges. A recent study measured BMI after GH treatment was ceased in 18 subjects. The BMI-SDS significantly increased at 6, 12, 18, and 24 months after cessation of GH therapy ($P = 0.039$, $P = 0.008$, $P = 0.003$, $P = 0.003$, respectively.) This data supports anecdotal evidence from parents, who report decreased energy, less ability to moderate mood, temperament and behaviour, a reduced ability to exercise and associated weight gain when GH treatment is stopped. [23]

3. The benefits to mental health

Dykens (1992) studied 21 adolescents and adults with PWS using the "Vineland Adaptive Behaviour Scales and Achenbach's Child Behaviour Checklist (CBCL)". This study demonstrated that while adaptive strengths became more pronounced with increasing age, "a relative weakness was found in socialization, most notably in coping skills. CBCL findings indicated that externalizing behaviours were particularly heightened in adolescence".[29] This confirms that adolescence is particularly challenging for the child with Prader-Willi syndrome.

A Japanese study found that rates of psychiatric disorders in PWS were significantly higher in young adults with PWS when comparing four different age groups: 2-5 years, 6-11 years, 12-17 years and 18-31 years. [27]

It has been found that adolescents treated with GH therapy experience a major reduction in depressive symptoms. [24] Therefore, as mental health disorders are highly prevalent in teenagers and adults with PWS, it would be of benefit to avoid the cessation of GH treatment at a time of greater vulnerability, when transitioning from adolescence to adulthood. [25, 26]

Another study assessed the long-term effect of GH treatment on the psychological well-being and Quality of Life (QoL) in an adult PWS group and found significant improvements with respect to baseline during the 2 year study.[28] Whitman (2002) studied the behavioural impact of growth hormone treatment for children and adolescents with PWS. Noting at the commencement of the study that the characteristics of PWS include "behavioural difficulties that increase in both quantity and severity over time', they completed a 2-year, controlled study with 54 children, genetically confirmed with PWS, who had not previously received growth hormone therapy. Their results showed a major reduction of depressive symptoms during the treatment period amongst the group aged 11 and older, and a lack of behavioural deterioration during this period. [24]

This clearly demonstrates that GH treatment in adolescence has benefits beyond the physical, which are of equal importance to the patient.

5. GH deficiency continues into adulthood

GH deficiency testing is no longer required for children with PWS because it is universally acknowledged from research that whilst children with PWS have a true disorder of GH secretion resulting in functional or evolving GH deficiency, only a minority of children would meet the requirements for severe GH deficiency during GH stimulation testing. [30] (There is also some disagreement amongst experts about what constitutes GH deficiency.) As evidence highlighting the positive effects of GH treatment in PWS mounted, PWS became a widely approved indication for GH treatment in children, without the need for GH testing. However, studies now show that adults with PWS continue to have GH deficiency. [31,32,33,34]

A recent study also concluded that GH deficiency in PWS increases with age. Cohen et al collected data from patient charts of children who had GH stimulation tests performed over a period of 12 years and found that biochemical GH deficiency was significantly associated with older age (r=0.45, P=0.02) and higher BMI z-score (r=0.45, P=0.02). Measurements were gathered until 15.5 years of age. [35]

As adults with PWS are likely to have the same health risks pertaining to non-PWS, GH deficient adults, we believe that the current age at which treatment ends is too early. When treatment ends, PWS patients are experiencing typical symptoms of GHD including negative changes in body composition and reduced stamina, whilst also coping with the pressures involved in the transition to adult life. Additionally, most adults with PWS are also deficient in sex steroid / sex hormone production which further increases the health risks associated with GH deficiency such as osteoporosis, fatigue and psychological depression.

We would like to note that the increasing GH deficiency may help to explain why some older children currently stop treatment before reaching the bone ages of 14 (female) or 16 (male) due to a failure to meet the current growth velocity criteria. This often results in appeals and additional stress for families.

Several studies have shown that GH treatment improves bone mineral density in children and adults with PWS. Bone fragility is characteristic of PWS. [36,37]

6. The challenges of adolescence for those with Prader-Willi syndrome

The adolescent years are challenging for most people, and additionally so for those with Prader-Willi syndrome, which is a unique and complex disorder, with multiple challenges.

We believe it is essential to maintain this positive effect of GH treatment for as long as possible into adulthood, particularly during early adulthood when a typically difficult period of transition is taking place. Many adolescents and young adults with PWS are transitioning into a residential care or supported living environment at this time, where support care workers usually require significant training in PWS to manage the dietary and behavioural needs of a young adult with PWS who is seeking more independence. The Prader-Willi Syndrome Association (NZ) assists in many cases where placements have been unsuccessful and rapid weight gain has occurred. The changes taking place at this time of life are not favourable to the cessation of GH treatment because the typical weight gain that occurs after treatment ceases [23] can be greatly exacerbated. Once weight has been gained, it can be extremely difficult to lose due to hypotonia, the high food seeking drive and the reduced ability and willingness to exercise. By prolonging the benefits of GH treatment for as long as possible, people with PWS and their families will experience a more positive transition into adulthood.

7. Treatment with GH should continue into adulthood

Though we are, in this submission, requesting a continuation of treatment until at least18 years of age, we are also preparing, for eventual lodgement with Pharmac, a submission seeking growth hormone treatment to continue for adults with Prader-Willi syndrome. A growing body of studies have documented the safety and efficacy of GH treatment in adults with PWS on body composition and in quality of life. [34, 38, 39, 40, 41] The Scandinavian Study, the largest study to date, found that the positive effects on body composition were maintained after 2 years of GH treatment and that peak expiratory flow increased by 12% ($P<0.001$).[41] In 2008, an Italian study investigated the effects of GH therapy on exercise capacity as well as body composition in adult patients, discovering beneficial effects on physical activity and agility. [42] A similar study in 2013 by Butler et al confirmed these benefits, but noted that after the 2nd year of the study in which patients were untreated, some of these benefits diminished, supporting the need for continuation of treatment. [43]

A study published in 2014 demonstrated that long-term GH treatment in adult PWS patients improves body composition, increases muscle strength and exercise tolerance independently from the GH secretory status.[44]

We believe the evidence above proves the many benefits of GH treatment for adolescents and adults with PWS, but response to GH therapy correlates to the duration of treatment.

In summary, we believe that the changes caused by cessation of treatment, both physical and psychological, needlessly compound the challenges of adolescence and that children with Prader-Willi syndrome should be able to continue to receive growth hormone treatment until they turn 18, and ideally beyond. The new International Consensus Guidelines state that "Treatment should be continued for as long as demonstrated benefits outweigh the risks."[8] We believe that we will soon see this guideline followed as other countries review their treatment criteria.

Budgetary impact of proposed changes

Prader-Willi syndrome is a rare condition. The incidence rate of PWS has been widely quoted as occurring between 1:16,000 and 1:25,000.

The birth rate in New Zealand is relatively stable and has averaged 62 000 in the last five years. Using an incidence rate of 1:16,000, we can expect between three and four infants to be born each year with Prader-Willi Syndrome. We would expect close to 100% uptake of GH treatment amongst this population.

Treatment costs have dropped significantly since GH criteria were last reviewed

The cost of GH therapy in New Zealand has reduced significantly since 2009, particularly with the introduction of the biosimilar Omnitrope in late 2014. Current costs are more than 60% lower than they were in 2009 when the access and exit criteria for this category were last reviewed, and almost one third lower again since the replacement of Genotropin with Omnitrope.

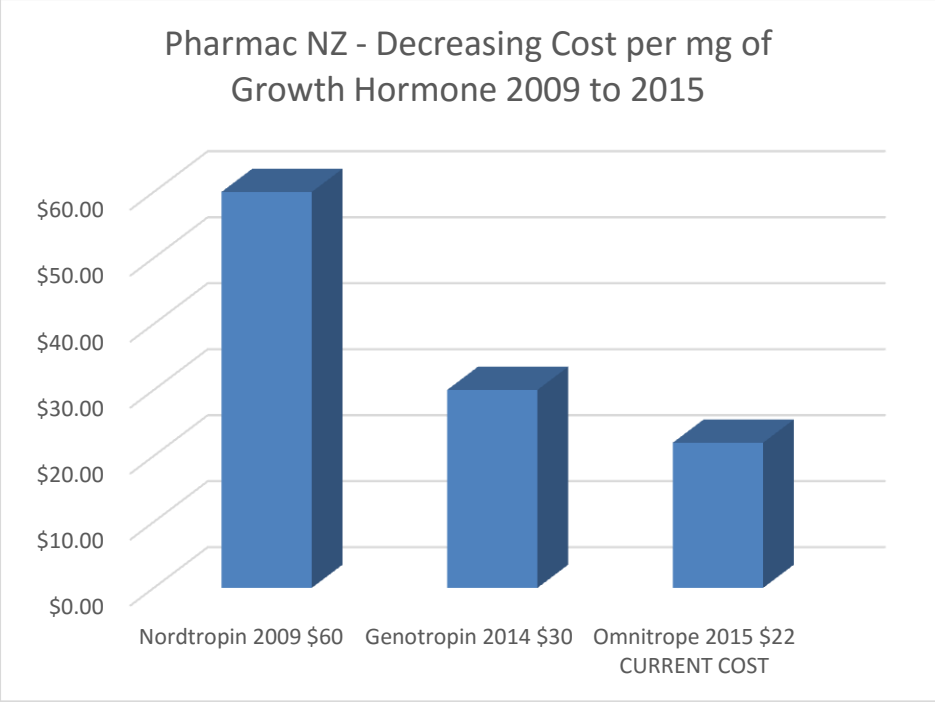

***Figure 3: Significant reduction in the cost of GH Treatment** (Costs published in current and historic Pharmac Pharmaceutical Schedules available online)*

Treatment costs for infants are minimal

Treatment costs for an infant of six months of age, receiving a daily dose of approximately 0.2mg per day, are approximately $1,600 per annum (based on a cost per mg of $22.00).

Given that infants can currently commence funded growth hormone treatment (subject to fulfilment of current entry criteria) at approximately 18 months of age, then the additional cost of four babies each year starting treatment one year earlier is $6,400 per annum in total (four additional patients @ $1,600 per annum). We believe this to be a negligible amount given the demonstrated long term benefits of starting this treatment in early infancy, and the savings made by the wider Health system in the longer term.

Cost for extending treatment until age 18

On average, patients are currently exiting the programme around the age of 15 years. At this age, patients are likely to be on a daily dose of approximately 1.4mg. To continue 4 patients each year, for an additional (on average) three years (from age 15 to age 18) at an average dose of 1.4mg per day (511 mg per year), will cost approximately $11,242 per patient, or a total (over an average of four patients) of less than $45,000. In reality, this cost is expected to be less as individual patient doses are likely to decrease by age 18, particularly for females.

Again, given the demonstrated benefits of continuing this treatment, particularly through adolescence, we believe this to be a negligible amount, and one that will be recovered by the wider Health system in savings of other treatments.

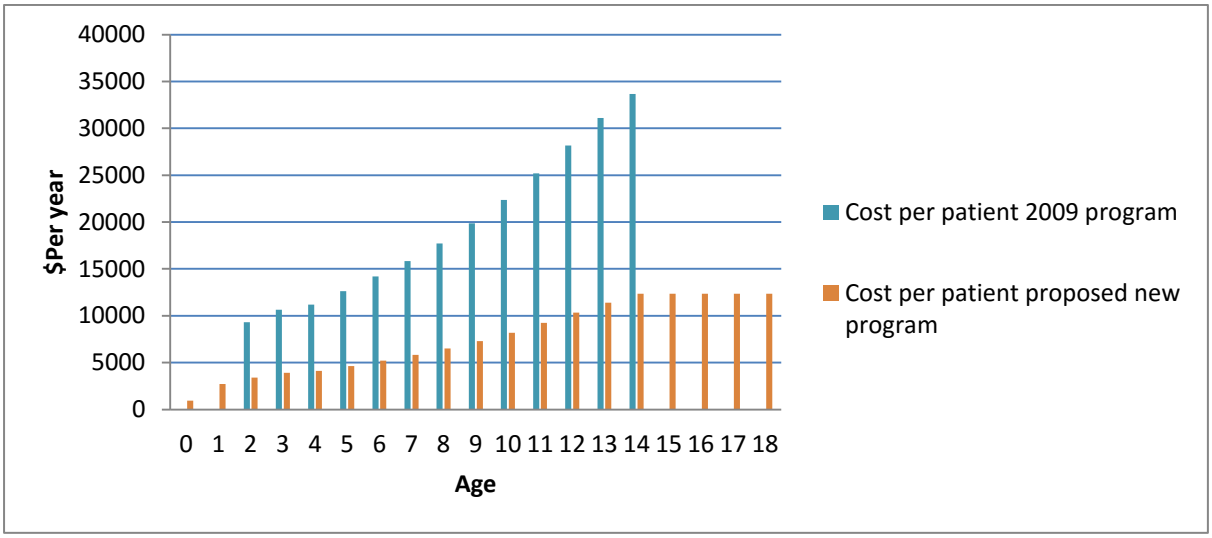

Figure 4: Comparison of current vs proposed GH program costs

In practice, GH dosage is usually calculated based on m² and may be individualized based on IGF-1 levels. For the purposes of creating this visual, approximate figures are based on a dose of 0.035mg/kg/day, using the 50th percentile CDC figures for female weight, and we have assumed the patient stays on the same dose for one year. Costs in the graph are based on $/mg published in the Pharmac Pharmaceutical Schedules for 2009 and 2015.

These two changes would create an estimated total increase in the growth hormone budget of approximately $51,000 per annum. Figures obtained from Pharmac show the total spend on GH for the 2013/14 year was $3,724,160 We note the estimated cost of implementing our proposed changes will be a global increase of less than 1.5%.

We note that increased costs are offset by the cost savings of switching from Genotropin to Omnitrope, which has bought a significant cost reduction to Pharmac.

Figures obtained from Pharmac below show that of the 291 patients receiving GH in 2013/14, only 31 were patients with PWS.

GH Special authority	Patient numbers 2013/14
Growth hormone deficiency in children	115
Short stature without growth hormone deficiency	80
Turner syndrome	52
Prader-Willi syndrome	31
Short stature due to renal insufficiency	13
Total:	291

The impact of widening access to GH

Two submissions raised the question of whether widening the access to GH for PWS would "open the door" to applications from other patient groups. The PWSA(NZ) finds this line of questioning surprising and unethical. We ask where would this fit within Pharmac's Factors for Consideration framework when making funding decisions?

Each application should be considered on its own merits, and we should not have to assess the effectiveness or cost of treatment for other patient groups in order to justify funding a treatment for PWS.GH has been used to treat PWS for over 20 years, with a large body of research over this period proving the effectiveness of GH treatment, and its impact on the health related quality of life for people with PWS. The body composition abnormalities in conjunction with hyperphagia and other metabolic defects are unique to PWS, and approving GH to treat body composition in PWS in no way gives "tacit approval" to treat body composition in other conditions.

As far as we are aware, none of the conditions mentioned (Cystic Fibrosis, Crohn's, Juvenile Arthritis, 18q syndrome, IBS) have current indications for GH treatment in New Zealand or internationally. Unlike PWS, research regarding the impact of GH in treating these conditions is in its infancy.

Thaker et al (2015) reviewed all available data on GH use in Cystic fibrosis and states: "*Recombinant growth hormone therapy is effective in improving the intermediate outcomes in height, weight and lean tissue mass when compared with no treatment. One measure of pulmonary function test showed moderate improvement at a single time point, but no consistent benefit was seen across all studies. No significant changes in quality of life, clinical status or side-effects were observed in this review. Long-term, well-designed randomised controlled trials of recombinant growth hormone therapy in people with cystic fibrosis are required prior to evaluation of human growth hormone treatment for routine use*"

Vortia et al (2011) reviewed the use of GH in Crohn's disease and states: "*Crohn's disease interacts with the GH-IGF-1 axis in important ways. Recent studies evaluating rhGH use in pediatric Crohn's disease have demonstrated some efficacy in reversing persistent linear growth delay but limited benefits in terms of improving mucosal disease and clinical disease activity. Larger studies of adequate power are needed to confirm a true benefit in terms of growth, to examine a potential benefit with regard to modification of disease activity, and to evaluate long-term risks*"

However, the PWSA(NZ) questions the relevance of this discussion in the consideration of widening access to somatropin under SA1451 Prader-Willi syndrome.

[NB. Budgetary information for adults beyond 18 years has not been included in this section of this submission, but we would like it to be noted that the adult maintenance dose required is much less, often reduced to 0.2mg. We would be happy to provide further data if required.]

The safety of growth hormone treatment for patients with Prader-Willi syndrome

Recent long running studies of GH treatment in large numbers of children [4], and a recent analysis of the KIGS Pfizer International Growth Database, all demonstrate that tolerability is high with minimal reported side effects. [45]

Growth hormone has been funded in New Zealand since 2005 and the Prader-Willi Syndrome Association (NZ) Inc. is not aware of any adverse events. Endocrinologists have already prescribed GH to at least four infants under one year of age in New Zealand, indicating that, in their professional judgement, the benefits of early treatment with GH outweigh the risks in this population.

Sleep disordered breathing in Prader-Willi syndrome

A submission was made that questioned the use of GH treatment in children under one year due to the breathing problems sometimes experienced by infants with PWS.

Sleep abnormalities are well documented in PWS and include altered sleep architecture, oxygen desaturation, and both central and obstructive sleep apnoea (OSA). The peak incidence of central sleep apnoea is in infancy, whereas the peak incidence of obstructive sleep apnoea occurs at 3 to 6 years, which is similar to the general population .[46] Apnoea has been shown to occur in 38% to 100% of patients with PWS, although many studies have shown that the breathing abnormalities during sleep are mild. [47,48,49,50]

Traditionally, sleep abnormalities are closely monitored during GH treatment due to concern there was a possible association between GH treatment, sleep abnormalities and sudden death.

However, despite these concerns, recent research shows that GH treatment does not increase the risk of sudden death in patients with PWS. [51,52,53,54,55] In fact, it has been shown that GH therapy improves oxygenation and cardiovascular function during sleep in patients with PWS. [56,57,58,59]

Studies have found that upper respiratory infections during the initiation phase of GH therapy can cause breathing problems in young children with PWS.[48,60] Some pulmonologists advocate monitoring with several nights of pulse oximetry during the initiation of GH therapy or during upper respiratory infections.

Lymphoid hyperplasia is related to high levels of IGF-I, [61] but research published in 2005 has shown that GH treatment does not change the prevalence or severity of OSA.[62] As a precaution, the GH consensus guidelines recommend that for the paediatric age range, IGF-I levels should be maintained within the upper part of normal range (1 to 2SDS) for healthy, age-matched normal individuals.[8]

In conclusion, close monitoring of IGF-1 levels, breathing, and sleep abnormalities is recommended throughout GH treatment and especially during respiratory illness.

"A lot of individuals with PWS tend to have sleeping abnormalities including apnea and oxygen desaturation. GH therapy strengthens muscles and improves arterial oxygenation and cardiovascular function during sleep in patients with PWS. Treatment with GH improves the response to carbon dioxide and increases ventilatory output and central inspiratory drive during sleep in patients with PWS."

Miller J, Wagner M 2013 Prader-Willi Syndrome and Sleep-Disordered Breathing PEDIATRIC ANNALS 42:10"

"Recent studies show either absence of change in sleep-disordered breathing or improved sleep cardiovascular function during hGH therapy."

Wolfgram PM, Carrel AL, Allen DB. 2013 Curr Opin Pediatr.25(4):509-514.

Parental commitment

We acknowledge that the benefits of growth hormone therapy for children with Prader-Willi syndrome are optimised when accompanied by a strict dietary regime and weight management programme. Further, treatment requires a commitment to daily administration of GH to patients.

We submit that parents of children with Prader-Willi syndrome are a very motivated group. Between 2004 and 2005, when publicly funded treatment was not available in New Zealand, up to 6 families privately funded GH treatment for their children, at significant financial cost, because they were convinced of the benefits. Anecdotal evidence seen by endocrinologists around the country would have to support this decision as being correct.

Over the last three years, we have had another 3 or more families privately fund growth hormone treatment for their young babies, to secure the benefits of early treatment, in the absence of publicly funded treatment. Again, this comes at significant financial cost.

The very vast majority of children with Prader-Willi syndrome live in families with advanced dietary management and food security. These are done at great personal cost to 'normal family life', but do ensure that the best possible environment is created to support the health of those with Prader-Willi syndrome.

We have previously been advised by Pharmac that compliance (i.e. the nightly injection with GH) is an issue amongst some patient groups. We do not believe it to be an issue amongst the Prader-Willi community due to our strength in belief of its power to change the course of a syndrome for which there are no other medical treatments available .

Summary

Research clearly demonstrates the efficacy of this treatment for children with PWS, and shows that the earlier in infancy the treatment is commenced, the more long-term benefits will be obtained.

The primary benefit of GH treatment for children with Prader-Willi syndrome is a significant improvement in body composition, with the resultant health benefits, and [combined with appropriate dietary controls] the almost total avoidance of obesity related health conditions. For this reason, GH treatment must be funded for all children with Prader-Willi syndrome, regardless of growth velocity.

Avoidance of obesity brings a substantial improvement in the quality of life of the patient, and drastically improves the patient's ability to participate fully in as 'normal' a life as possible. A randomised controlled study released in August this year has shown that children who are treated with GH have a greater health related quality of life than untreated children. [63]

The improved health outcomes brought about by GH treatment will result in lower health costs in other areas, particularly obesity related costs. The cost of providing GH treatment is small in the context of the overall budget for GH treatment, and also small in relation to the costs that are otherwise likely to be incurred by the overall health system, should these children become obese.

Increasing amounts of research, and international best practice, also support the safety of commencement of GH treatment in early infancy, which provides a range of positive effects.

Given the significant benefits of treatment, we believe treatment should continue until a patient turns at least18 years of age.

Removing the requirement for slow growth, commencing GH therapy earlier and continuing until the child attains at least18 years of age will provide significant health benefits to individuals with PWS. It will provide treatment to a subset of the PWS population who currently have significant unmet health needs.

We seek fair treatment and a better quality of life for all people with PWS.

References

1. Lionti T, Reid SM, White SM, Rowell MM. **A population-based profile of 160 Australians with Prader-Willi syndrome: Trends in diagnosis, birth prevalence and birth characteristics.** Am J Med Genet 2014 Part A. 9999:1–8
2. Butler MG. **Prader-Willi Syndrome: Obesity due to Genomic Imprinting.** Curr Genomics. 2011;12(3):204–215.
3. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. **Prader-Willi syndrome**. Genet Med. 2012;14(1):10–26.
4. Bakker NE, et al **Eight Years of Growth Hormone Treatment in Children With Prader-Willi Syndrome: Maintaining the Positive Effects.** J Clin Endocrinol Metab. 2013 Oct;98(10):4013-4022
5. Colmenares A, Pinto G, Taupin P, Giuseppe A, Odent T, Trivin C, Laborde K, Souberbielle JC, Polak M. **Effects on growth and metabolism of growth hormone treatment for 3 years in 36 children with Prader-Willi syndrome.** Horm Res Paediatr. 2011 Feb;75(2):123-30. doi: 10.1159/000319709.
6. Carrel AL, Myers SE, Whitman BY, Eickhoff J, Allen DB. **Long-term growth hormone therapy changes the natural history of body composition and motor function in children with prader-willi syndrome.** J Clin Endocrinol Metab. 2010 Mar;95(3):1131-6.
7. de Lind van Wijngaarden RF, Siemensma EP, Festen DA, Otten BJ, van Mil EG, Rotteveel J, Odink RJ, Bindels-de Heus GC, van Leeuwen M, Haring DA,Bocca G, Houdijk EC, Hoorweg-Nijman JJ, Vreuls RC, Jira PE, van Trotsenburg AS, Bakker B, Schroor EJ, Pilon JW, Wit JM, Drop SL, Hokken-Koelega AC. **Efficacy and safety of long-term continuous growth hormone treatment in children with Prader-Willi syndrome.** J Clin Endocrinol Metab. 2009 Nov;94(11):4205-15. doi: 10.1210/jc.2009-0454. Epub 2009 Oct 16.
8. Deal CL, Tony M, Höybye C, Allen DB, Tauber M, Christiansen JS; 2011 Growth Hormone in Prader-Willi Syndrome Clinical Care Guidelines Workshop Participants. **Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome.** J Clin Endocrinol Metab. 2013 Jun;98(6):E1072-87. doi: 10.1210/jc.2012-3888. Epub 2013 Mar 29
9. Scheermeyer, E., Hughes, I., Harris, M., Ambler, G., Crock, P., Verge, C. F., Craig, M. E., Bergman, P., Werther, G., van Driel, M., Davies, P. S. and Choong, C. S. (2013), **Response to growth hormone treatment in Prader–Willi syndrome: Auxological criteria versus genetic diagnosis.** Journal of Paediatrics and Child Health, 49: 1045–1051
10. Festen DA, de Lind vW, van Eekelen M, Otten BJ, Wit JM, Duivenvoorden, HJ, Hokken-Koelega AC**. Randomized controlled GH trial: effects on anthropometry, body composition and body proportions in a large group of children with Prader-Willi syndrome.** Clin Endocrinol (Oxf). 2008;69(3):443–451.
11. Whitman B, Carrel A, Bekx T, Weber C, Allen D, Myers S. **Growth hormone improves body composition and motor development in infants with Prader-Willi syndrome after six months.** J Pediatr Endocrinol Metab. 2004;17:591–600.
12. Eiholzer U, L'Allemand D, Schlumpf M, Rousson V, Gasser T, Fusch C. **Growth hormone and body composition in children younger than 2 years with Prader-Willi syndrome.** J Pediatr. 2004;144(6):753–758.
13. Myers SE, Carrel AL, Whitman BY, Allen DB. **Sustained benefit after 2 years of growth hormone on body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome.** J Pediatr. 2000;137(1):42–49
14. Festen DA, Wevers M, Lindgren AC, Böhm B, Otten BJ, Wit JM, Duivenvoorden HJ, Hokken-Koelega AC. **Mental and motor development before and during growth hormone**

treatment in infants and toddlers with Prader-Willi Syndrome. Clin Endocrinol (Oxf). 2008 Jun;68(6):919-25. Epub 2007 Nov 19.

15. Nyunt O, Harris M, Hughes I, Huynh T, Davies PS, Cotterill AM. **Benefit of early commencement of growth hormone therapy in children with Prader-Willi syndrome.** J Pediatr Endocrinol Metab.2009;22(12):1151–1158.
16. Colmenares A, Pinto G, Taupin P, Giuseppe A, Odent T, Trivin C, Laborde K, Souberbielle JC, Polak M. **Effects on growth and metabolism of growth hormone treatment for 3 years in 36 children with Prader-Willi syndrome.** Horm Res Paediatr. 2011 Feb;75(2):123-30. doi: 10.1159/000319709.
17. Carrel AL, Myers SE, Whitman BY, Eickhoff J, Allen DB. **Long-term growth hormone therapy changes the natural history of body composition and motor function in children with prader-willi syndrome.** J Clin Endocrinol Metab. 2010 Mar;95(3):1131-6
18. Myers SE, Whitman BY, Carrel AL, Moerchen V, Bekx MT, Allen DB. **Two years of growth hormone therapy in young children with Prader-Willi syndrome: physical and neurodevelopmental benefits.** Am J Med Genet A. 2007 Mar 1;143A(5):443-8.
19. Carrel AL, Moerchen V, Myers SE, Bekx MT, Whitman BY, Allen DB 2004 **Growth hormone improves mobility and body composition in infants and toddlers with Prader-Willi syndrome.** J Pediatr 145:744–749
20. Miller JL, Lynn CH, Driscoll DC, Goldstone AP, Gold JA, Kimonis V, Dykens E, Butler MG, Shuster JJ, Driscoll DJ. **Nutritional phases in Prader-Willi syndrome.** Am J Med Genet A. 2011 May;155A(5):1040-9.
21. Siemensma EP1, Tummers-de Lind van Wijngaarden RF, Festen DA, Troeman ZC, van Alfen-van der Velden AA, Otten BJ, Rotteveel J, Odink RJ, Bindels-de Heus GC, van Leeuwen M, Haring DA, Oostdijk W, Bocca G, Mieke Houdijk EC, van Trotsenburg AS, Hoorweg-Nijman JJ, van Wieringen H, Vreuls RC, Jira PE, Schroor EJ, van Pinxteren-Nagler E, Willem Pilon J, Lunshof LB, Hokken-Koelega AC. **Beneficial effects of growth hormone treatment on cognition in children with Prader-Willi syndrome: a randomized controlled trial and longitudinal study.** J Clin Endocrinol Metab. 2012 Jul;97(7):2307-14. doi: 10.1210/jc.2012-1182. Epub 2012 Apr 16.
22. Coupaye M, Lorenzini F, Lloret-Linares C, Molinas C, Pinto G, Diene G, Mimoun E, Demeer G, Labrousse F, Jauregi J, Laurier V, Basdevant A, Polak M,Thuilleaux D, Tauber M, Poitou C. **Growth hormone therapy for children and adolescents with Prader-Willi syndrome is associated with improved body composition and metabolic status in adulthood.** J Clin Endocrinol Metab. 2013 Feb;98(2):E328-35. doi: 10.1210/jc.2012-2881. Epub 2013 Jan 2.
23. Oto Y1, Tanaka Y, Abe Y, Obata K, Tsuchiya T, Yoshino A, Murakami N, Nagai T. **Exacerbation of BMI after cessation of growth hormone therapy in patients with Prader-Willi syndrome.** Am J Med Genet A. 2014 Mar;164A(3):671-5
24. Whitman BY1, Myers S, Carrel A, Allen D. **The behavioral impact of growth hormone treatment for children and adolescents with Prader-Willi syndrome: a 2-year, controlled study. Pediatrics.** 2002 Feb;109(2):E35.
25. Skokauskas N, Sweeny E, Meehan J, Gallagher L. **Mental health problems in children with Prader-Willi Syndrome.** J Can Acad Child Adolesc Psychiatry. 2012 Aug;21(3):194-203.
26. Sinnema M, Boer H, Collin P, Maaskant MA, van Roozendaal KE, Schrander-Stumpel CT, Curfs LM. **Psychiatric illness in a cohort of adults with Prader-Wili Syndrome.** Res Dev Disabil. 2011 Sep-Oct;32(5):1729-35. doi: 10.1016/j.ridd.2011.02.027. Epub 2011 Mar 31

27. Hiraiwa R, Maegaki Y, Oka A, Ohno K. **Behavioral and psychiatric disorders in Prader-Willi syndrome: a population study in Japan.** Brain Dev. 2007 Oct;29(9):535-42. Epub 2007 Feb 20
28. Bertella L, Mori I, Grugni G, Pignatti R, Ceriani F, Molinari E, Ceccarelli A, Sartorio A, Vettor R, Semenza C. **Quality of life and psychological well-being in GH treated, adult patients: a longitudinal study.** J Intellect Disabil Res. 2007 Apr;51(Pt 4):302-11.
29. Dykens EM, Hodapp RM, Walsh K, Nash LJ. **Adaptive and maladaptive behaviour in Prader-Willi syndrome.** J Am Acad Child Adolesc Psychiatry 1992 Nov;31(6):1131-6
30. Eiholzer U, Bachmann S, l'Allemand D. **Is there a growth hormone deficiency in Prader-Willi syndrome? Six arguments to support the presence of hypothalamic growth hormone deficiency in Prader-Willi Syndrome.** Horm Res. 2000;53 Suppl 3:44-52.
31. Grugni G, Marostica E, Crinò A, Marzullo P, De Nicolao G, Sartorio A. **Deconvolution-based assessment of pituitary GH secretion stimulated with GHRH+arginine in Prader-Willi adults and obese controls.** Clin Endocrinol (Oxf). 2013 Aug;79(2):224-31. doi: 10.1111/cen.12142. Epub 2013 Apr 5.
32. Grugni G, Crinò A, Bertocco P, Marzullo P. **Body fat excess and stimulated growth hormone levels in adult patients with Prader-Willi Syndrome.** Am J Med Genet A. 2009 Feb 15;149A(4):726-31. doi: 10.1002/ajmg.a.32713.
33. van Nieuwpoort IC, Sinnema M, Castelijns JA, Twisk JW, Curfs LM, Drent ML **The Gh/IGF-1 axis and pituitary function and size in adults with Prader-Willi Syndrome.** Horm Res Paediatr. 2011;75(6):403-11. doi: 10.1159/000323442. Epub 2011 Jan 27.
34. Höybye C. **Endocrine and metabolic aspects of adult Prader-Willi syndrome with special emphasis on the effect of growth homone treatment.** Growth Horm IGF Res. 2004 Feb;14(1):1-15.
35. Cohen M, Harrington J, Narang I, Hamilton J. **Growth hormone secretion decreases with age in paediatric Prader-Willi syndrome.** Clin Endocrinol (Oxf). 2014 Dec 11. doi: 10.1111/cen.12694.
36. Longhi S, Grugni G, Gatti D, Spinozzi E, Sartorio A, Adami S, Fanolla A, Radetti G. **Adults with Prader-Willi syndrome have weaker bones: effect of treatment with GH and sex steroids.** Calcif Tissue Int. 2015 Feb;96(2):160-6. doi: 10.1007/s00223-014-9949-1. Epub 2015 Jan 11.
37. Khare M, Gold JA, Wencel M, Billimek J, Surampalli A, Duarte B, Pontello A, Galassetti P, Cassidy S, Kimonis VE. **Effect of genetic subtypes and growth hormone treatment on bone mineral density in Prader-Willi Syndrome.** J Pediatr Endocrinol Metab. 2014 May;27(5-6):511-8. doi: 10.1515/jpem-2013-0180
38. Sode-Carlsen R, Farholt S, Rabben KF, Bollerslev J, Schreiner T, Jurik AG, Christiansen JS, Hoybye C**. One year of growth hormone treatment in adults with Prader-Willi syndrome improves body composition: results from a randomized, placebo-controlled study.**J Clin Endocrinol Metab. 2010;95(11):4943–4950
39. Sode-Carlsen R, Farholt S, Rabben KF, Bollerslev J, Schreiner T, Jurik AG, Frystyk J, Christiansen JS, Höybye C. **Growth hormone treatment for two years is safe and effective in adults with Prader-Willi Syndrome.** Growth Horm IGF Res. 2011 Aug;21(4):185-90. doi: 10.1016/j.ghir.2011.05.002. Epub 2011 Jun 12
40. Mogul HR, Lee PD, Whitman BY, Zipf WB, Frey M, Myers S, Cahan M, Pinyerd B, Southren AL. **Growth hormone treatment of adults with Prader-Willi syndrome and growth hormone deficiency improves lean body mass, fractional body fat, and serum triiodothyronine without glucose impairment: results from the United States multicenter trial.** J Clin Endocrinol Metab. 2008 Apr;93(4):1238-45. doi: 10.1210/jc.2007-2212. Epub 2008 Jan 22.

41. Sode-Carlsen R, Farholt S, Rabben KF, Bollerslev J, Schreiner T, Jurik AG, Christiansen JS, Höybye C. **Growth hormone treatment in adults with Prader-Willi syndrome: the Scandinavian study.** Endocrine. 2012 Apr;41(2):191-9. doi: 10.1007/s12020-011-9560-4. Epub 2011 Nov 12
42. Gondoni LA, Vismara L, Marzullo P, Vettor R, Liuzzi A, Grugni G **Growth hormone tgherapy improves exercise capacity in adult patients with Prader-Willi Syndrome.** J Endocrinol Invest. 2008 Sep;31(9):765-72.
43. Butler MG, Smith BK, Lee J, Gibson C, Schmoll C, Moore WV, Donnelly JE. **Effects of growth hormone treatment in adults with Prader-Willi syndrome.** Growth Horm IGF Res. 2013 Jun;23(3):81-7. doi: 10.1016/j.ghir.2013.01.001. Epub 2013 Feb 19.
44. Lafortuna CL, Minocci A, Capodaglio P, Gondoni LA, Sartorio A, Vismara L, Rizzo G, Grugni G. **Skeletal muscle characteristics and motor performance after 2-year growth hormone treatment in adults with prader-willi syndrome.** J Clin Endocrinol Metab. 2014 May;99(5):1816-24. doi: 10.1210/jc.2013-3607. Epub 2014 Jan 28
45. Craig ME, Cowell CT, Larsson P, Zipf WB, Reiter EO, Albertsson WK, Ranke MB, Price DA. **Growth hormone treatment and adverse events in Prader-Willi syndrome: data from KIGS (the PfizerInternational Growth Database).** Clin Endocrinol (Oxf). 2006; 65(2):178–185.
46. Miller J, Wagner M. **Prader-Willi syndrome and sleep-disordered breathing**. Pediatr Ann. 2013 Oct;42(10) 200-204
47. Bruni O, Verrillo E, Novelli L, Ferri R. **Prader- Willi syndrome: sorting out the relationships between obesity, hypersomnia, and sleep apnea.** Curr Opin Pulm Med. 2010;16(6):568-573.
48. Miller JL, Shuster J, Theriaque D, Driscoll DJ, Wagner M. **Sleep disordered breathing in infants with Prader-Willi syndrome during the first 6 weeks of growth hormone therapy: a pilot study.** J Clin Sleep Med. 2009;5(5):448- 453.
49. Verrillo E, Bruni O, Franco P, et al. **Analysis of NREM sleep in children with Prader-Willi syndrome and the effect of growth hormone treatment.** Sleep Med. 2009;10(6):646-650.
50. Williams K, Scheimann A, Sutton V, Hayslett E, Glaze DG. **Sleepiness and sleep disordered breathing in Prader-Willi syndrome: relationship to genotype, growth hormone therapy, and body composition.** J Clin Sleep Med. 2008;4(2):111-118.
51. Al-Saleh S, Al-Naimi A, Hamilton J, et al. **Longitudinal evaluation of sleep-disordered breathing in children with Prader-Willi Syndrome during 2 years of growth hormone therapy.** J Pediatr. 2013;162(2):263-8.e1.
52. DeMarcantonio MA, Darrow DH, Gyuricsko E, Derkay CS. **Obstructive sleep disorders in Prader-Willi syndrome: the role of surgery and growth hormone.** Int J Pediatr Otorhinolaryngol. 2010;74(11):1270-1272.
53. Meinhardt U, Christiansen JS, Farholt S, et al. **The efficacy and safety of long-term norditropin treatment in children with Prader-Willi syndrome.** Horm Metab Res. 2013;45(7):532-536.
54. Nagai T1, Obata K, Tonoki H, Temma S, Murakami N, Katada Y, Yoshino A, Sakazume S, Takahashi E, Sakuta R, Niikawa N. **Cause of sudden, unexpected death of Prader-Willi syndrome patients with or without growth hormone treatment.** Am J Med Genet A. 2005 Jul 1;136(1):45-8.
55. Tauber M, Diene G, Molinas C, Hebert M. **Review of 64 cases of death in children with Prader-Willi syndrome (PWS).** Am J Med Genet A. 2008;146:881–887

56. Wolfgram PM, Carrel AL, Allen DB**. Long-term effects of recombinant human growth hormone therapy in children with Prader-Willi syndrome.** Curr Opin Pediatr. 2013;25(4):509-514.
57. Katz-Salamon M, Lindgren AC, Cohen G. **The effect of growth hormone on sleep-related cardio-respiratory control in Prader-Willi syndrome.** Acta Paediatr. 2012;101:643–648.
58. Myers SE, Carrel AL, Whitman BY, Allen DB. **Physical effects of growth hormone treatment in children with Prader-Willi syndrome.** Acta Paediatr Suppl. 1999;88:112–114.
59. Lindgren AC, Hellstrom LG, Ritzen EM, Milerad J. **Growth hormone treatment increases CO(2) response, ventilation and central inspiratory drive in children with Prader-Willi syndrome.** Eur J Pediatr. 1999;158:936–940
60. Festen DA, de Weerd AW, van den Bossche RA, et al. **Sleep-related breathing disorders in prepubertal children with Prader- Willi syndrome and effects of growth hormone treatment**. J Clin Endocrinol Metab. 2006;91(12):4911-4915
61. Chernausek SD, Backeljauw PF, Frane J, Kuntze J, Underwood LE**. Long-term treatment with recombinant insulin-like growth factor(IGF)-I in children with severe IGF-I deficiency due to growth hormone insensitivity.** J Clin Endocrinol Metab. 2007;92(3):902–910.
62. Whitman, Myers. 2013**. Prader-Willi syndrome and growth hormone therapy: take a deep breath and weigh the data.** J Pediatr. 2013 Feb;162(2):224-6.
63. Bakker NE1, Siemensma EP, van Rijn M, Festen DA, Hokken-Koelega AC. **Beneficial Effect of Growth Hormone Treatment on Health-Related Quality of Life in Children with Prader-Willi Syndrome: A Randomized Controlled Trial and Longitudinal Study.**
Horm Res Paediatr. 2015 Aug 13. [Epub ahead of print]

Appendix

Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. J Clin Endocrinol Metab. , 2013