

Original Articles

An Update on the Indications of Growth Hormone Treatment under Hospital Authority in Hong Kong

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Abstract Since 1978, Growth hormone (GH) has been used to treat patients with GH deficiency in Hong Kong. In 1998, the Hospital Authority expanded the use of GH in children with Turner syndrome and chronic renal failure before transplantation. Two additional indications for GH treatment, Prader-Willi syndrome and short stature homeobox-containing gene disorders have been approved in 2012. The objective of this paper is to discuss the recommendations of GH treatment for children and adolescents with these conditions in Hong Kong.

Key words Growth hormone treatment; Hospital Authority

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Background

Growth hormone (GH) is an expensive drug and its use under funding by the government has to be justified with substantial benefits and evidences. Human pituitary derived GH was used to treat patients with GH deficiency and was provided by the Hong Kong government from 1978 till 1985. Creutzfeldt-Jacob disease due to prion-contaminated human pituitary derived GH was reported in 1985. Recombinant human GH was approved for use by the Food and Drug Administration (FDA) of the United States (US) in the same year and its use was supported by our government since 1989. With the introduction of GH therapy for non-GH deficient patients, GH therapy for Turner syndrome and chronic renal failure before transplantation was approved by the Hospital Authority (HA) in Hong Kong in 1998. It is used mainly for growth promotion. Since then, more indications have been approved by the FDA and European Agency. Hospital Authority approves two additional indications for GH treatment including Prader-Willi syndrome (PWS) and short stature homeobox-containing (SHOX) gene disorder in 2012. The objective of this paper is to discuss the recommendations of GH treatment for children and adolescents with these conditions in Hong Kong. The

recommendations are based mainly on literature review, expert opinions and consensus, with consideration of the local circumstances. The use of GH in other conditions is beyond the scope of this paper due to unresolved controversies.

GH is an essential hormone for normal growth in children. It increases growth by a direct action on the growth plates and by production of insulin-like growth factors (especially IGF-1), mainly in the liver. It is also important in the metabolism of proteins, lipids and carbohydrates as well as bone health. In addition to the growth-promoting effect, GH treatment also aims to improve body composition in Prader-Willi syndrome.

Growth Hormone Deficiency

GH deficiency occurs at an incidence of 1:4,000-10,000. This can be congenital or acquired, isolated or associated with other pituitary hormones deficiency. Profound hypoglycaemia and prolonged jaundice may occur in neonatal period. Features of micropenis, midline craniofacial abnormalities and positive family history are suggestive of congenital GH deficiency. For acquired conditions, there may be history of brain tumour, cranial irradiation, head trauma, surgery or central nervous system infection.

Children suspected of GH deficiency should have clinical and auxological assessments together with exclusion of other systemic causes of short stature like hypothyroidism, chronic systemic disease, Turner syndrome and skeletal disorders. Insulin-like growth factor -1 (IGF-1) should be measured but low concentration is also found in children suffering from malnutrition, hypothyroidism and liver disease. GH provocative tests can be performed with pharmacological agents such as glucagon, arginine, L-dopa and insulin to diagnose GH deficiency. An international guideline reached the consensus that peak GH concentration less than 10 ug/L in two stimulation tests was considered abnormal. The cut-off level is assay-dependent and the value needs to be revised as different assays methods are used in our local laboratories.^{1,2} In the presence of pathological causes such as brain tumour and multiple pituitary hormone deficiency, one abnormal provocative test is sufficient for the diagnosis. Sex hormone priming is necessary before GH stimulation test to reflect GH secretion potential in peripubertal children.³ This is recommended in girls aged >11.5 years and boys aged >13 years who are still in prepubertal stage

or have only early signs of puberty.⁴ Magnetic resonance imaging (MRI) of the brain with particular attention to the hypothalamic-pituitary region should be performed in any child diagnosed with GH deficiency.²

Studies have demonstrated that GH treatment increases the height velocity and final adult height of children with GH deficiency.⁵ The recommended dose is 0.5-1 IU/kg/week (0.025-0.05 mg/kg/day). GH should be started as soon as possible after the diagnosis is made and an intracranial tumour excluded by MRI as studies show that children beginning treatment at the youngest ages have the most favorable adult height outcomes. Higher doses during puberty (2 IU/kg/week) may be considered in adolescents with late diagnosis and diminished period of time for catch-up.⁶ However it may not be necessary if height is maximised before the onset of puberty.² Thyroid function should be monitored before and during treatment as central hypothyroidism may be unmasked by GH treatment and there may be increased conversion of T4 to T3.⁷

The Eligibility Criteria for GH treatment in GH deficiency include:

1. Growth hormone deficiency is diagnosed as based on abnormal slow growth velocity (decreasing height centiles) and evidence of biochemical growth hormone deficiency.
2. A twelve months tumour-free period following the completion of treatment for brain tumour is observed.

Turner Syndrome

Turner syndrome (TS) is characterised by short stature, dysmorphism, cardiac, renal anomalies and primary hypogonadism in phenotypic females. It is a common chromosomal condition occurring at a frequency of about 1 in 2000-2500 live female births and is caused by partial or complete X chromosome monosomy.⁸ Most Turner patients do not have classical GH deficiency. It is believed that haploinsufficiency of one copy of the SHOX gene located within the pseudoautosomal region on the distal short arm of the X (and Y) chromosomes is primarily responsible for the growth problems in Turner patients.⁹ Growth failure generally begins in utero, continues into infancy and childhood, and is accentuated by the absence of pubertal growth spurt. The reported mean final height of Chinese patients with TS in Hong Kong was 142 cm¹⁰ compared to 147 cm observed in Northern European.¹¹

Studies including randomised, controlled trials have repeatedly demonstrated that GH treatment is effective in

promoting height gain and improves the final adult height.^{12,13} Average final height gain was around 5 to 8 cm over a treatment period ranging from 5.5 to 7.6 years although response to treatment can be variable. The recommended dose is 0.375 mg/kg/week divided daily (0.045-0.05 mg/kg/day).^{14,15}

The optimal age of starting GH treatment is not defined. A recent randomised, controlled 2-year study demonstrated that early initiation of GH treatment as young as 9 months of age prevented the growth failure that typically occurred in the first few years of life.¹⁶ The Turner Syndrome Consensus Study Group recommended that GH should be considered as soon as growth failure (decreasing height centiles) is noted.¹⁵ This may also allow sex hormone treatment for pubertal induction at a more physiological age (~12 years of age) rather than postponing it until at least 14 years of age with the intention of maximising the duration of GH treatment and increasing the final height. Furthermore, there is increasing concern about the potential negative effects of delayed estrogen replacement on psychosocial development, bone mineral accrual, uterine development, sexual maturation, self-esteem, and possibly cardiovascular risk.^{15,17}

Oxandrolone at a dose of 0.05 mg/kg/day; maximum 2.5 mg/day may be given in conjunction with GH in girls who are older than 8-9 years of age and have extreme short stature to optimise height gain. Liver function should be monitored.¹⁵ A recent randomised study showed that in patients receiving GH treatment, late induction of puberty has no added advantage to the final height when oxandrolone was given.¹⁸

Hypothyroidism and scoliosis with or without kyphosis are common in patients with Turner syndrome. Thyroid function and assessment of scoliosis should be performed before and during GH treatment regularly. The risk of glucose intolerance, slipped capital femoral epiphysis and intracranial hypertension is also increased and should be monitored.⁶

Eligibility Criteria of GH treatment in Turner syndrome include:

1. The girl has abnormal slow growth velocity (decreasing height centiles); and
2. Turner syndrome is genetically proven

Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is characterised by severe neonatal hypotonia, short stature, and hyperphagia after

infancy leading to morbid obesity and hypogonadism. It is caused by the lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13.¹⁹ The incidence is around 1 in 25,000 births.²⁰ Currently, 48 patients less than 18 years of age are recorded by the Clinical Genetic Counselling Service (unpublished data) in Hong Kong.

Growth failure occurs early from prenatal period. It is generally thought that patients with PWS have evidence of disturbed hypothalamic control of GH secretion and growth hormone deficiency is universal in PWS.¹⁹ The mean spontaneous adult height has been reported as 162 cm in boys and 150 cm in girls from European population.²¹ No local data on adult height is available in Hong Kong.

The recommended dose of GH in PWS is 21 IU/m²/week (1 mg/m²/day or ~0.035 mg/kg/day) with a maximum of 8 IU/day (2.7 mg/day).¹⁴ In those with mature skeleton (bone age ≥14 years in female and ≥16 years in male), a dose of 0.12 IU/kg/week is recommended. In obese subjects, it is suggested to calculate the dose based on body surface area instead of body weight to avoid excessive dosing and to minimise the risk of side effects. Randomised controlled study using GH with a dose of 21 IU/m²/week demonstrated a significant increase in growth velocity and lean body mass, decrease in percent body fat and improvement in bone mineral density. GH therapy improves overall muscle tone, physical strength, and agility.²² Studies on long-term use again showed that it normalised height SDS and improved waist circumference SDS and body mass index (BMI) SDS_{PWS} without significant adverse side effects.²³ In a recent study where children having GH treatment initiated before 2 years of age (range 4-32 months, mean 13±6 months) showed improvement in body composition, motor function, height and lipid profiles with no adverse effect.²⁴ Growth hormone therapy in adult PWS was considered effective and safe in a 12 month duration study.²⁵ Recommendation on GH treatment after 18 years old would be considered when substantial beneficial evidences are available.

PWS patients are at risk of a range of co-morbidities and these should be monitored before and during GH treatment.

1. *Obstructive sleep apnoea and central hypoventilation during sleep*

The increased risk of obstructive sleep apnoea (OSA) is related to obesity, micrognathia, small naso-oropharynx, sticky secretions, hypotonia and adenotonsillar hypertrophy. Unexpected deaths occur in PWS patients with or without GH treatment. Most of them were related to complicated course of relatively

mild respiratory tract infection. There are concerns on the potential contribution of upper airway obstruction to the risk of death in PWS patients receiving GH. The greatest risk occurs within the first 9 months of GH treatment.²⁶ Hence it is recommended to start with a lower dose at 5-7 IU/m²/week and increase gradually to 21 IU/m²/week over the first weeks and months. Insulin-like growth factor-1 (IGF-1) level was demonstrated to have a role in worsening OSA and this should be monitored at least twice every year and maintained within two standard deviations (SD) above the mean.¹⁹ During treatment, it is important to watch out for development or worsening of sleep apnoea. Sleep study and ear, nose and throat evaluation should be performed before and within 6 months after starting GH.²⁷ Treatment should be instituted for sleep disorder and delay of GH therapy considered in severe OSA until improvement is demonstrated.

2. *Hypothyroidism*

Central or primary hypothyroidism may occur in patients with PWS.²⁸ Thyroid function should be checked before and regularly during GH treatment.

3. *Scoliosis*

Scoliosis with or without kyphosis is common in patients with PWS¹⁹ and is probably related to hypotonia and obesity. Assessment is required before initiation of and during GH treatment. Although the rapid increase in linear growth rate during GH treatment may exacerbate the problem, withholding GH is not necessary in most situations.

4. *Carbohydrate intolerance*

In PWS, the risk of Type 2 diabetes mellitus is increased. Regular monitoring of glucose tolerance with fasting sugar, HbA1c, insulin and OGTT (particularly if positive family history of DM) is mandatory.

5. *Hypogonadism*

Hypogonadism, both central and peripheral in origins, is a common feature¹⁹ and sex hormone treatment is usually indicated. The dosing and timing should reflect as far as possible the process of normal puberty.

6. *Secondary adrenal insufficiency*

Adrenal insufficiency due to hypothalmo-pituitary axis dysregulation was demonstrated and this might account for sudden death in PWS. Investigating morning adrenocorticotrophic hormone and cortisol and repeated assay at time of critical illness are useful screening tests.¹⁹

To optimise the outcome of GH treatment in PWS, control of the food environment and behaviour are vital to

control body weight and to prevent morbid obesity. The complex multisystem involvement means that a multi-disciplinary management approach is required to reduce morbidity and mortality, and to improve the quality of life.

Eligibility criteria of GH treatment in PWS include:

1. The patient is less than 18 years of chronological age; and
2. PWS is genetically proven; and
3. Evaluation including sleep study was performed and treatment was instituted for any sleep-related breathing disorders; and
4. The patients do not have uncontrolled morbid obesity (body weight greater than 200% of ideal body weight for height)

A list of Response criteria of GH treatment in PWS was set up in the Australia guideline. It includes:²⁹

In Non-mature skeleton:

1. Maintaining or improving height centile;
2. Maintaining or improving BMI SDS;
3. Maintaining or improving waist circumference (SDS or waist/height ratio);
4. Maintaining or improving age standardised measures of body composition using dual energy X-ray absorptiometry or bioelectrical impedance.

In Mature skeleton:

1. Maintaining or improving BMI or BMI SDS;
2. Maintaining or improving waist circumference (SDS or waist/height ratio);
3. Maintaining or improving weight SDS;
4. Maintaining or improving standardised measures of body composition.

Short Stature Homeobox-containing Gene Disorders

The SHOX gene was discovered in 1997. It encodes a homeodomain transcription factor responsible for long bone growth and is located in the pseudoautosomal regions at the distal ends of the X and Y chromosomes.⁹ The gene is responsible for growth deficit in patients with Turner syndrome, 50-90% of patients with Leri-Weill dyschondrosteosis and 2-15% of patients with idiopathic short stature.³⁰ Normal growth requires two functional copies of the gene. Hence, growth impairment can occur if one copy of the SHOX gene has been inactivated by mutation or deletion (haploinsufficiency).

Children with SHOX deficiency have growth failure

starting in infancy and the mean adult height was -2.2 SDS.³⁰ The phenotypes of individuals with SHOX gene disorders can be highly variable, ranging from short stature without obvious dysmorphism to severe mesomelic skeletal dysplasia (shortening of the forearms and lower legs).³¹ A scoring system based on clinical features to identify the most appropriate subjects to test for SHOX deficiency has been developed.³²

The overall prevalence of SHOX gene disorders in patients with short stature is 1 in ~2500.³¹ In Hong Kong, about 8 patients less than 18 years of age have been diagnosed by the Clinical Genetics Counselling Service of the Department of Health, Hong Kong (unpublished data). With increased awareness and availability of GH treatment, the number of patients diagnosed with SHOX gene disorders is expected to rise.

Based on the effectiveness of GH treatment on Turner syndrome, GH was used in patients with SHOX gene disorders. The recommended dose is 1 IU/kg/week (0.045-0.05 mg/kg/day).¹⁴

A randomised, controlled, multicentre study showed that GH was effective in promoting height gain of 0.9 SDS over 2 years.³³ Adult height would be increased by 1.1 SDS when compared with baseline and the response was similar to that observed in Turner girls.³⁴ In a study using combination of GH with long-acting gonadotrophin releasing hormone analog aiming to delay the puberty, the adult height SDS was -1.7 as compared with -2.5 SDS in the control group.³⁵ More evidences should be sought before regarding it as a standard treatment strategy.

Eligibility criteria of GH treatment in SHOX gene disorders include:

1. The height is less than -2.32 SDS (1st percentile) for age and sex; and
2. The patient has abnormal slow growth velocity (decreasing height centiles); and
3. A SHOX gene disorder is genetically proven

Chronic Renal Insufficiency before Renal Transplantation

A diagnosis of chronic kidney disease (CKD) requires the presence of kidney damage and/or glomerular filtration rate (GFR) <60 ml/min/1.73 m² for a period of at least 3 months.³⁶ The condition is rare in children and the estimated incidence in individuals under 20 years of age is around 12 cases per million.³⁷

Growth failure is common in patients with CKD and the

adult height is less than 2 SDS below the mean in about half of the patients. Factors including protein-calorie malnutrition, acid-base disturbances, hyperparathyroidism, glucocorticoid treatment, derangements in the GH-IGF axis and GH insensitivity contribute to growth failure.³⁸

Studies including multicenter, randomised, placebo-controlled trials have shown that GH is effective in improving height velocity.³⁹ The adult height may be increased by approximately 7-11 cm.^{40,41}

Before starting GH treatment, the metabolic derangements such as nutritional deficiency and acid-base disturbances should be corrected as far as possible. GH is given at a dose of 28-30 IU/m²/week (0.045-0.05 mg/kg/day)¹⁴ and is generally considered safe without adverse effects on renal function. However, careful monitoring of renal function is mandatory. It is suggested to perform X-ray hips before initiating GH treatment and to stop GH in the presence of active renal osteodystrophy (hyperparathyroidism) as slipped capital femoral epiphysis is more common in patients with CKD.

Clinical trials have demonstrated growth promoting effect and safety of GH therapy in children after renal transplantation. However the recommendation on the duration and time of starting GH requires further research study.⁴²

Eligibility Criteria of GH treatment in CKD include:

1. The patient has irreversible renal insufficiency before renal transplantation; and
2. The creatinine clearance is less than 60 ml/min/1.73 m²; and
3. The patient has short stature with height less than -1.88 SDS (3rd percentile) for age and sex; and
4. Growth failure persists beyond 3 months despite treatment of nutritional deficiencies and metabolic abnormalities; and
5. The patient must be under the care of a paediatric specialist with expertise in nephrology.

End-point of Growth Hormone Treatment

In conditions where GH is used for growth promotion, the treatment should be stopped when the patient has nearly reached final height. This is indicated by skeletal maturity with bone age reaching 14 years in female and 16 years in male. The height velocity will be less than 2 cm over a year.

Consideration of stopping GH should also be made when the patient reaches target height range, in conditions of

Turner syndrome, SHOX deficiency and CKD.

In PWS, GH treatment should be discontinued when the patient reaches 18 years of chronological age. Recommendation on GH treatment after 18 years old would be considered when substantial beneficial evidences are available.

Side Effects of Growth Hormone

With institution of long-term GH therapy, it is important to monitor the possible adverse effects of treatment. Pseudotumour cerebri (benign intracranial hypertension) may develop and present as headache and papilloedema. GH should be stopped and when the patient recovers, GH is restarted at a lower dose (one fourth of the previous dose) and then stepped up gradually to the full dose over a few weeks. Slipped capital femoral epiphysis and worsening of existing scoliosis tend to occur in rapidly growing children and may require surgical correction. These may be considered as a consequence of rapid growth rather than a direct side effect of growth hormone and continuation of GH treatment is recommended in general.⁴³ GH may induce carbohydrate intolerance in children with compromised insulin secretion. Hence checking fasting plasma glucose and HbA1c before and during GH therapy especially for those at risk including Turner syndrome and obese patients is recommended.⁴⁴ Diabetes mellitus remains as contraindication to GH therapy except in children with growth hormone deficiency. Other side effects of GH treatment include prepubertal gynaecomastia, oedema, arthralgia, myalgia and local reaction at the injection site.

There is concern that GH treatment might increase the risk of tumour progression or appearance of a second neoplasm as GH and IGF-1 have mitogenic and anti-apoptotic activities.⁴⁵ Epidemiological studies have suggested possible association between IGF-1 level in the high-normal range and cancers of the breast, prostate and colon.⁴⁵ An United Kingdom retrospective analysis of cancer incidence and mortality rates in adults who received human pituitary-derived GH as children during the period from 1959 to 1985 suggested an increased incidence of colon cancer and an increased mortality rate from colon cancer and Hodgkin's disease.⁴⁶ However, there is no conclusive evidence to support a role of GH in cancer pathogenesis.⁴³ In the KIGS (Pfizer International Growth Database) study on 58 603 patients from 1987 to 2008, the risk of developing cancer relative to that expected in the normal population was not increased.⁴⁷ Few studies

indicated that GH treatment does not increase recurrence of brain tumour in those whose primary lesion has been successfully treated.⁴⁸ The National Cooperative Growth Study (NCGS) on 54,996 children over 20 years reported that the risk of leukaemia was not increased but the risk of second malignancies in patients previously treated with irradiation was higher as compared with age-matched general population.⁴⁹ Nevertheless, the presence of an active malignancy is a contraindication to GH use and it is recommended to start GH treatment one year after the completion of tumor treatment with no further evidence of tumour recurrence or growth.⁴³ Monitoring of IGF-1 level is recommended to ensure that it is maintained within age appropriate limits.⁴³ If IGF-1 level is more than two standard deviation above the mean, the dose of GH should be titrated down to bring IGF-1 level closer to the normal range. In children with increased malignancy risks such as Fanconi anaemia, Bloom syndrome, neurofibromatosis and XY Turner syndrome, careful consideration should be made about starting GH treatment.³ Further information on the safety of childhood GH treatments would be available when the 3-year SAGhE (Safety and Appropriateness of Growth hormone treatments in Europe) Study ends in May 2012. A lifespan surveillance of adverse events in GH treated patients, with concerted effort from worldwide endocrine societies, is required to conclude the long-term safety of GH therapy.⁵⁰

Monitoring for Efficacy and Safety of Growth Hormone Treatment

Children on GH treatment should be monitored for height, weight, pubertal development, and adverse effects at 3-6 month intervals. Bone age should be obtained periodically to reassess height prediction and consideration of intervention of puberty development.

Traditionally the dosage of GH treatment has been based on the body weight or surface area. Recent studies have shown that titrating GH dosing based on IGF-1 levels is clinically feasible and has taken into account the individual variation of GH sensitivity. Serum IGF-1 concentrations should be maintained within the physiological range. The possible cancer risk, accelerated skeletal maturation and earlier onset puberty associated with high IGF-1 level and high GH dose should be attended to.^{45,51}

Response to treatment can be very variable and is related to dose, age, parental height, compliance, intercurrent illness and other concurrent endocrine therapies. Molecular

factors including the structure and concentration of GH receptors would also affect the response. Suggested criteria for poor first-year response include growth velocity that fails to increase by at least 3 cm/yr.⁵² Using the NCGS data, curves of height velocity response to GH during the first year of treatment with standard daily GH doses in prepubertal children, aged 2-14 year at initiation of GH treatment for GH deficiency, idiopathic short stature and Turner syndrome have been constructed to assist clinicians in assessing a patient's first-year growth response. Height velocity 1 SD below the mean on these plots is considered a "poor" response.⁵³

For standard reference, the present paper suggests that adequate growth response is indicated by improvement in height SDS by 0.3 for chronological age or increment of height velocity by 2 cm after 6 months or maximum one year trial of GH. In patients with poor growth response or failure to achieve normal-range IGF-1, drug compliance or co-existing pathology such as hypothyroidism should be explored. Prader-Willi syndrome patients not satisfying at least one of the listed response criteria are also regarded as treatment failure and GH therapy should be discontinued.²⁹

Health-related Quality of Life in Growth Hormone Treated Patients

The evidences indicated the significant benefit of GH therapy in growth promotion in these disease groups, with the additional effectiveness in changes in body composition in PWS. To evaluate the improvement of outcome in GH

treated patients, it is also important to take into consideration the effects of height gain on physical health and quality of life including the need of daily injections, psychological wellbeing, potential adverse effects and treatment costs.⁵⁴

A review of studies on health-related quality of life observed a small gain in utility for individuals receiving GH treatment.⁵⁵ The Canadian study in adult Turner patients randomised to GH therapy and no GH treatment in the growing period showed normal scores on physical and mental component scales using the SF-36 method and there was no significant difference between the two groups.⁵⁶

A research to study the quality of life in the GH treated patients in our local population is important to measure the quality of medical care.

Conclusions

Under the Hospital Authority in Hong Kong, GH therapy is currently indicated in GH deficiency, Turner syndrome, chronic renal insufficiency before transplantation, Prader-Willi syndrome and SHOX gene disorders. The dosages of GH treatment in these conditions are summarised in Table 1. As GH is an expensive drug and not without side effects, treatment with GH should always be initiated and monitored by a paediatrician with special expertise in managing growth hormone disorders in children. Children should be evaluated every 3-6 months. As these patients usually have multiple health problems, a multi-disciplinary management approach is important to reduce morbidity, mortality and to improve quality of life.

Table 1 Summary of the indications and dosages of growth hormone treatment

| Indications | Growth hormone dosage | | |
|--|--|-------------------------------------|---|
| | mg / kg / day | IU / kg / week | Dose / m ² |
| Growth hormone deficiency | 0.025-0.05 mg/kg/day | 0.5-1 IU/kg/week | 4.5-7.5 mg/m ² /week |
| Turner syndrome | 0.045-0.05 mg/kg/day | 1 IU/kg/week | 4.5-9.5 mg/m ² /week |
| SHOX gene disorders | 0.045-0.05 mg/kg/day | 1 IU/kg/week | 4.5-9.5 mg/m ² /week |
| Chronic renal insufficiency before renal transplantation | 0.045-0.05 mg/kg/day | 1 IU/kg/week | 28-30 IU/m ² /week 4.5-9.5 mg/m ² /week |
| Prader-Willi syndrome | Non-mature skeleton: start with a lower dose and increase gradually to 0.035 mg/kg/day; maximum 2.7 mg/day Mature skeleton: 0.005 mg/kg/day | Mature skeleton: 0.12 IU/kg/week | Non-mature skeleton: start with a lower dose at 0.23-0.33 mg/m ² /day or 5-7 IU/m ² /week and increase gradually to 1 mg/m ² /day or or 21 IU/m ² /week; maximum 2.7 mg/day or 8 IU/day |

SHOX: short stature homeobox-containing

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