

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Human growth hormone in children (Review of TA No. 42)

Draft scope

Appraisal objectives¹:

To review and update as necessary guidance to the NHS in England and Wales on the clinical and cost effectiveness of human growth hormone (somatropin) in the treatment of growth deficiencies and other growth failure in children which was issued in May 2002².

Background

Growth hormone (GH) is produced by the anterior pituitary gland. It is essential for normal growth in children and acts by increasing growth, both by a direct action on the growth plates (the area between the epiphysis and the diaphysis within which bone growth occurs) and via the production of insulin-like growth factors in the liver. GH also generally affects metabolism and tissue growth.

Growth failure in children can be a result of GH deficiency (GHD). Also, growth failure is a prominent feature in children with chronic renal insufficiency (CRI), Turner syndrome (TS), Prader-Willi syndrome (PWS), Short stature homeobox-containing gene (SHOX) deficiency and in short children born small for gestational age (SGA).

GHD is the commonest endocrine disorder presenting with short stature; it is estimated that 25% of children with height <-3 SDS have GHD. The frequency of GHD is estimated at 1 in 3,500 to 4,000. Most children with GHD (50-70%) have an idiopathic isolated deficiency in GH (IGHD), but hypopituitarism can also occur as part of combined or multiple pituitary hormone deficiencies. Children with GHD who remain untreated have an untreated final height of 134-146cm in males and 128-134cm in females.

TS, which is caused by the complete or partial lack of one X chromosome, has an incidence of 1 in 1,500 to 2,500 live born females. The majority (80-100%) of affected girls have short stature with a reduction in final height of 20-21 cm, and a mean untreated final height of 136-147cm.

¹ DH remit: To advise on the clinical and cost effectiveness of the use of human growth hormone in treatment of growth deficiencies and other growth failure in children.

² Guidance on the use of human growth hormone in children (No. 42, May 2002)⁷

The growth failure in CRI is thought to be multi-factorial, with one of the factors thought to be reduced sensitivity to GH rather than decreased GH levels.

PWS affects 1 in 15,000-25,000 live births, and most have deletions involving the paternal 15th chromosome. Mean final height is approximately 154cm in males and 145-149 cm in females.

The SHOX gene is located on both the X and Y chromosome and plays an important role in the growth and maturation of arm and leg bones. SHOX deficiency results from a deletion or mutation of the SHOX gene and the resultant changes in the function of the SHOX protein. SHOX deficiency is believed to be the basis of the short stature in TS, the Léri-Weill syndrome, Langer syndrome and in some individuals with idiopathic short stature.

Children are born SGA for maternal, placental, or foetal reasons. It is estimated that 12% of children born SGA fail to reach the normal height range.

GH therapy is currently the mainstay treatment to correct growth failure for children with short stature listed above. In these groups of children, there are no other active treatment options to increase stature. Treatment with GH has been reported to increase final height by between 3 and 12 cm. For girls with TS, oxandrolone may be added to GH treatment regimens. In the UK, conservative management strategies for CRI include diet guidance and nutritional supplementation. The first four groups of children (GHD, TS, CRI and PWS) are included in NICE technology appraisal guidance no 42.² A marketing authorisation for the treatment of short stature due to SGA and SHOX deficiency was granted after the NICE guidance was issued.

The Technology

Recombinant human growth hormone (somatropin) is produced by recombinant DNA technology and has a sequence identical to that of pituitary-derived human growth hormone. The recommended dose varies according to the condition being treated.

Somatropin currently has a marketing authorisation in the UK for the following conditions:

- growth disturbance in children due to insufficient secretion of growth hormone (GHD)
- growth failure in girls due to gonadal dysgenesis (Turner syndrome [TS])
- growth retardation in prepubertal children due to chronic renal insufficiency (CRI)

- children with Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing.
- growth disturbance (current height SDS -2.5 and parental adjusted height SDS, -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 SD, who failed to show catch-up growth (HV SDS <0 during the last year) by 4 years of age or later.
- growth failure associated with SHOX deficiency, as confirmed by DNA analysis

Currently seven manufacturers have marketing authorisations for somatropin in the UK for the indications shown in the table below.

Manufacturer (Product)	GHD	TS	CRI	PWS	SGA	SHOX
Eli Lilly & Co Ltd (Humatrope)	✓	✓	✓		✓	✓
Ferring Pharmaceuticals (UK) (Zomacton)	✓	✓				
Ipsen Ltd (NutropinAq)	✓	✓	✓			
Novo Nordisk Ltd (Norditropin Simple Xx)	✓	✓	✓		✓	
Pfizer Ltd (Genotropin)	✓	✓	✓	✓	✓	
Sandoz Limited (Omnitrope)	✓	✓	✓	✓	✓	
Merck Serono (Saizen)	✓	✓	✓		✓	

Intervention(s)	Recombinant human growth hormone (somatropin)
Population(s)	<p>Children with growth disturbance as per licensed indication for each preparation available for the following populations:</p> <ul style="list-style-type: none"> • children with growth hormone deficiency (GHD) • girls with Turner syndrome (TS) • prepubertal children with chronic renal insufficiency (CRI) • children with Prader-Willi syndrome (PWS) • children born small for gestational age (SGA) • children with growth failure associated with SHOX deficiency, as confirmed by DNA analysis
Standard comparators	No treatment
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • Health related quality of life • final height gained • height standard deviation score-height relative to the distribution of height in children of the same chronological age (or bone age) • growth velocity • growth velocity standard deviation score-growth velocity relative to the distribution of growth in children of the same chronological age (or bone age) • body composition for GHD and PWS (BMI, lean mass, percent body fat) • adverse effects
Economic analysis	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>The time horizon for the economic evaluation should reflect the nature of each of the conditions being treated</p> <p>Costs for any diagnostic tests related to the treatment decision should be included in the economic analysis.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p>

<p>Other considerations</p>	<p>The interventions will be appraised according to their marketing authorisation</p> <p>Where information is available, consideration will be given to the effect of somatropin on biochemical and metabolic markers.</p>
<p>Related NICE recommendations</p>	<p>Related Technology Appraisals:</p> <p>NICE technology appraisal guidance No 42 - Growth hormone deficiency (children) (May 2002)</p> <p>NICE technology appraisal guidance No. 64 - Growth hormone deficiency (adults) (August 2003)</p>

Current NICE guidance

1. Recombinant human growth hormone (somatropin) treatment is recommended for children with proven clinical diagnosis of growth hormone (GH) deficiency supported by appropriate auxological, biochemical and radiological investigations.
2. GH treatment is recommended for children with Turner syndrome (TS). The following issues should be taken into consideration in order to maximise the benefit from this treatment:
 - diagnosis and treatment at earliest age possible
 - appropriate timing and use of oestrogen therapy
3. GH treatment is recommended for pre-pubertal children with chronic renal insufficiency (CRI) providing :
 - nutritional status has been optimised
 - metabolic abnormalities have been optimised
 - steroid treatment has been reduced to a minimum.
4. GH treatment is recommended for children with Prader-Willi syndrome.
5. GH treatment should, in all circumstances, be initiated and monitored by a paediatrician with special expertise in the management of children with GH disorder. Continuation of treatment can be maintained under an agreed shared-care protocol with a general practitioner.
6. GH treatment should be re-evaluated and normally discontinued if there is a poor response to treatment, defined as the increase in growth velocity of less than 50% from baseline, in the first year of therapy. Ongoing response should be evaluated against expected growth based on standard growth charts. Therapy should be normally stopped when final height is approached and growth velocity is less than 2 cm total growth in 1 year. Persistent and uncorrectable problems with adherence to treatment should also be taken into account as part of re-evaluation of treatment. In Prader-Willi syndrome evaluation of response to therapy should also consider body composition.
7. After attainment of final height, GH therapy will normally be discontinued, but it should not be discontinued by default. The decision to stop treatment should either be made by a paediatrician with special expertise in the management of children with GH disorders in consultation with patient and carers, or therapy should continued until revaluation by an adult endocrinologist has been undertaken. The transition to adult care for people with GH disorders will require a close collaboration between the responsible clinicians.
8. In children with CRI, GH treatment should be stopped after renal transplantation. It should not normally be re-started until at least 1 year after renal transplantation to allow time to ascertain whether catch-up growth will occur.

	9. The use of GH therapy in children with idiopathic short stature is currently not licensed, and therefore it was not considered as part of this appraisal.
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Questions for consultation

A view from Consultees and Commentators would be appreciated on

- How SGA should be defined?
- Whether growth monitoring should be included as a standard comparator?
- Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality?