NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

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

Draft scope

Appraisal objectives[1]:

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 2002[2].

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 affects carbohydrate and lipid metabolism, nitrogen 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 children with short 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 124-146cm in males and 128-134cm in females.

TS, which is caused by the 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 original 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)'

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. It is unclear whether those affected have GHD.

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 can be born with SGA for maternal, placental, or fetal reasons. It is estimated that 12% of children born with 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 the current NICE technology appraisal.[2] A marketing authorisation for the treatment of short stature due to SGA was granted after the NICE guidance was issued.

An additional group of children that may be relevant to this appraisal are children with idiopathic short stature. Idiopathic short stature is the term used when children are very short compared with others in their age cohort, for unknown or hereditary reasons. This group is heterogeneous, made up of patients whose short stature cannot be explained by an underlying pathology. Idiopathic short stature is not a disease and therefore specific diagnostic criteria cannot be used to determine who has ISS. Because of the arbitrary cut-off point of a peak HGH level of 10 µg/l for GHD, it is probable that some children diagnosed as having GHD could be categorised as having idiopathic short stature and conversely some individuals currently diagnosed as having idiopathic short stature may be have GHD.

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),
- growth failure associated with SHOX deficiency, as confirmed by DNA analysis

Currently there is no market authorisation for the use of somatropin for idiopathic short stature.

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)	✓	✓	✓		✓	
Pfizer Ltd (Genotropin)	✓	✓	✓	✓	✓	
Sandoz Limited (Omnitrope)	✓	✓	✓	✓	✓	
Merck Serono (Saizen)	✓	✓	✓		✓	

Intervention(s)	Recombinant human growth hormone (somatropin)
Population(s)	Children with growth disturbance as per licensed indication for each preparation available
Standard comparators	Management strategies without somatropin.
Outcomes	The outcome measures to be considered include: • 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) • cognitive function • health-related quality of life • adverse effects of treatment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for the economic evaluation should reflect the nature of each of the conditions being treated Costs for any diagnostic tests related to the treatment decision should be included in the economic analysis. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	The interventions will be appraised according to their marketing authorisation.
Related NICE recommendations	Related Technology Appraisals: NICE technology appraisal guidance No 42 - Growth hormone deficiency (children) (May 2002) NICE technology appraisal guidance No. 64 - Growth hormone deficiency (adults) (August 2003)

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. n and Clinical Excellence ed appraisal of The use of human growth hormone (somatropin) in 9. The use of GH therapy in children with idiopathic short 10. 11

	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.

Questions for consultation

A view from Consultees and Commentators would be appreciated on

- whether this topic should be split into more than one appraisal because of the large number of indications for somatropin. If yes, how should the indications be grouped?
- how standard comparators should be defined.
- the evidence available to define the optimal dosing strategies in the management of patients in transition from paediatric to adult care.
- the evidence available to define the optimal starting age and length of GH treatment for girls with TS.
- the evidence available to define the optimal treatment strategies of GH treatment for children with PWS.