

**Treatment of Children with
Recombinant Human Growth Hormone
(r-hGH)**

**Shared Care Guidelines
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**Jeremy Kirk & Gary Butler
on behalf of the**

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and Diabetes (BSPED)**

SHARED CARE of PATIENTS on GH THERAPY

Background

Although linear growth is influenced by a number of factors, growth hormone (GH) plays a predominant role with both direct and indirect effects on the epiphyseal growth plate. It also affects carbohydrate and lipid metabolism, nitrogen metabolism and tissue growth.

Pituitary extracted growth hormone (pit-hGH) was first used as a treatment for growth hormone deficiency (GHD) in children in 1958. As supplies were reliant on the availability of cadaveric pituitaries, only the most severely affected children were treated using standard doses eg 4 U (1.3 mg) thrice weekly by intra-muscular injection.

Pit-hGH was withdrawn in 1985 when a number of treated patients developed Creutzfeldt-Jacob disease (CJD). In the same year the first biosynthetic hGH (met-hGH, somatrem) became available in the UK, followed by natural sequence r-hGH (somatropin) in 1988. All GH used in the UK is now r-hGH, manufactured using E-coli or mammalian vectors and is structurally, chemically and biologically identical to pituitary-source hGH.

GH currently has a product licence in the UK for the following conditions:

- GH-deficiency (GHD): paediatric and adult licences.
- Turner syndrome (TS)
- Chronic renal insufficiency (CRI)
- Prader-Willi syndrome (PWS)
- Small for gestational age (SGA)

The first four paediatric indications were included in the NICE technology assessment of May 2002 and have been ratified. The SGA licence was not granted until 2003 (ie. after the NICE review) and is likely to be dealt with in the subsequent NICE review (due 2007-8).

Absence of NICE guidance is not, however, a reason for refusing GH therapy for licensed indications. Jane Kennedy MP, Minister of State for Quality and Patient Safety stated, on 7 December 2005 at the NICE Conference: 'It is not acceptable for the local NHS to cite a lack of NICE guidance as the sole reason for not providing a treatment. A key role of the NHS has been, and will continue to be, to make decisions about the use of new pharmaceuticals. NICE does not exist to "kite mark" all the drugs which are licensed for use in the UK. Therefore, the NHS will have to continue to make informed decisions about the use of these drugs.'

http://www.dh.gov.uk/NewsHome/Speeches/SpeechesList/SpeechesArticle/fs/en?CONTENT_ID=4125786&chk=dCNfdo

LICENSED INDICATIONS

Growth hormone deficiency (GHD)

GHD is the commonest endocrine disorder presenting with short stature; it is estimated that 25% of children with a height < -3 SDS have GHD. The frequency of GHD is estimated at 1 in 3,500-4,000, although a milder phenotype may occur in up to 1 in 2,000.

The commonest causes of GHD are given below.

Congenital	Acquired
<ul style="list-style-type: none"> • Midline embryonic defect: <i>septo-optic dysplasia (SOD), cleft palate, pituitary aplasia/hypoplasia.</i> • Transcription factor mutations: <i>GHI, Pit-1, PROPI, HESXI.</i> 	<ul style="list-style-type: none"> • Pituitary/hypothalamic tumour: <i>craniopharyngiomas, germinoma, pinealoma.</i> • Trauma: <i>surgery, perinatal, RTA.</i> • Infiltration; <i>histiocytosis, lymphoma, leukaemia</i> • Infection: <i>bacterial, viral, fungal</i> • Irradiation: <i>intracranial, nasopharyngeal tumours. Cranial or cranio-spinal irradiation in acute leukaemia.</i> • Temporary failure: <i>emotional deprivation, peri-pubertal or hypothyroidism.</i> • Idiopathic

Most (50-70%) have an isolated deficiency of GH (IGHD), but hypopituitarism can also occur as part of combined (CPHD) or multiple (MPHD) pituitary hormone deficiencies: TSH, ACTH, LH, FSH, prolactin and/or diabetes insipidus.

The clinical diagnosis of GHD includes short stature, slow growth (a documented height velocity (HV) below the 25th centile for at least one year), and delayed bone age. In severe GHD the HV may be < 4 cm/year. Affected children have increased skinfolds and appear plump with immature facies, small hands, feet and genitalia. Milder forms may remain unrecognised until the child is older and other clinical manifestations at this stage are rare.

Random GH levels are of little no diagnostic value, although measurement of IGF-1 and its binding protein IGFBP-3 may be used as an indirect indicator of GH-secretion. The diagnosis of GHD is confirmed by a peak plasma GH level below ~20 mU/L (dependant on GH assay) to 1 or 2 provocative tests (dependant on diagnosis). Tests commonly used include using insulin hypoglycaemia (ITT), glucagon, clonidine and arginine, although in view of the potential dangers of ITT, this test is not recommended for use outside large experienced tertiary centres.

Historical GHD untreated groups have an untreated final height (FH) of 134 –146 cm in males and 128 –134 cm in females. With GH treatment FH is improved by 8.7 –10.7 cm in boys, & 7.7 – 9.5 cm in girls.

Turner syndrome (TS)

Although TS affects ~ 3% of all female fetuses, a high miscarriage rate of affected fetuses produces an incidence of 1 in 1,500-2,500 live born females. Approximately half have 45XO; the remainder show other X-chromosome abnormalities or mosaicism. The majority (80-100%) have short stature with a reduction in FH of 20-21 cm, and a mean untreated FH of 136-147 cm.

Patients show mild intra-uterine growth retardation, poor growth during infancy and childhood, and blunted pubertal growth spurt. Dysmorphic features are often present, but variable.

There are few controlled trials of GH in TS, but short-term increase in height velocity is 2.4-2.8 cm/year, with improvement in FH of ~5 cm.

Chronic renal insufficiency (CRI)

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.

GH is recommended for pre-pubertal children with chronic renal insufficiency, providing:

- Nutritional status has been optimized.
- Metabolic abnormalities have been optimized.
- Steroid therapy has been reduced to a minimum.

GH results in an increase in HV of ~ 4 cm/y in the first year. Improvement in FH appears to be 3-9 cm.

Prader-Willi syndrome (PWS)

This affects 1 in 15,000-25,000 live births, and most patients have deletions involving the paternal 15th chromosome. The syndrome is characterised by hyperphagia, hypogonadism, short stature, dysmorphism, hypoventilation and behavioural problems. Mean FH is approximately 154 cm in males and 145-149 cm in females. It is unclear whether these patients are truly GHD or not, although GH therapy results in improvements in both height (approximately 1 SD in the first year) body composition, and muscle strength/tone.

There is limited data on FH in GH-treated patients with PWS; one study indicates an increase of 11 cm in males and 9.8 cm in females. There have, however, been a number of reports of sudden death in PWS patients treated with GH, especially if patients are severely obese.

Small for gestational age (SGA)

These children are a heterogeneous group, as children can be born SGA for a variety of different reasons: maternal, placental, or fetal. It is estimated that 12% of children born SGA fail to catch up into the normal range. GH is licensed for children born SGA (birthweight and/or length below -2 SD (2nd centile), who fail to show catch-up growth (height velocity < 0 during the last year) by 4 years of age or later, and who are short both compared to their peers (height < -2.5 SD) and parents (parental adjusted height < -1 SD).

Short term growth is increased with GH, and a number of studies have now demonstrated significant improvements in FH ~12 cm.

Other diagnoses

GH accelerates growth in the short term in short normal children but produces little improvement in final height. GH is not currently licensed for this indication. Research is continuing in other conditions such as skeletal dysplasia, juvenile rheumatoid arthritis and other severe conditions to assess the response to treatment with GH but treatment on the indication of growth failure is merited in some children.

Recommended doses of GH

<u>Diagnosis</u>	<u>Doses: $\mu\text{g}/\text{kg}/\text{day}$</u>	<u>$\text{mg}/\text{m}^2/\text{day}$</u>
GH-deficiency (GHD)	23-39	0.7-1.0
Turner syndrome (TS)	45-50	1.4
Chronic renal insufficiency (CRI)	45-50	1.4
Prader-Willi syndrome (PWS)	25*	1.0*
Small for gestational age (SGA)	35-66#	1.0-2.0#

* Daily maximum 2.7 mg/day.

Current UK study (NESGAS) commences higher dose for the 1st year of GH therapy

There are currently six manufacturers of r-hGH in the UK

Product	Manufacturer
Genotropin	Pfizer
Norditropin Simplexx	Novo Nordisk
Saizen	Serono
Zomacton	Ferring
Humatrope	Lilly
Nutropin	Ipsen

Biogeneric GH may also become available in the future.

The product licence for each manufacturer is as follows:

Manufacturer (product)	GHD	TS	CRI	PWS	SGA
Ferring (Zomacton)	X	X			
Ipsen (Nutropin)	X	X	X		
Lilly (Humatrope)	X	X	X		
Novo (Norditropin)	X	X	X		X
Pfizer (Genotropin)	X	X	X	X	X
Serono (Saizen)	X	X	X		

As a polypeptide, GH must be administered by injection; the subcutaneous route is now used. There are a number of different GH devices available, which broadly fall into 2 groups:

- Needled devices: pen, needle & syringe,
- Needle-free devices.

Manufacturer (product)	Pen device	Pre-filled Needle/syringe	Needle-free device
Ferring (Zomacton)			X
Ipsen (Nutropin)	X		
Lilly (Humatrope)	X		
Novo (Norditropin)	X		
Pfizer (Genotropin)	X	X	X
Serono (Saizen)	X		X

Starting GH

As children receiving GH therapy require regular assessment of progress by specialists in child growth, full discharge of the patients from the hospital to the GP is therefore not possible. A system of shared care, involving both primary and back-up care is therefore necessary. These guidelines outline the probable areas of responsibility of the hospital and the GP for patients who have shared care.

- At the outset of treatment, and ideally before, the GP will receive a referral letter, giving full clinical details and full details of treatment. The dosage required of GH and other therapy will be determined by the specialist.
- Although current GH products have been shown to be equipotent in terms of growth effect, there is also evidence that patient choice of device, training and support (in the hospital and at home) and home delivery improve compliance with therapy. The decision regarding the choice of GH product needs to be made by the specialist unit and is based on a number of factors other than cost alone. It is also important that any changes in the brand should be made by the specialist centre, since training in a new

injection technique may be required. It also avoids duplication of reporting should side effects occur.

- The patient and their family will be instructed in injection technique, use of injection devices, storage and management of GH supplies by the Regional Specialist Paediatric Endocrine Nurse or deputy, who will liaise with the GP and/or practice nurse.

Responsibilities for monitoring of GH therapy by the specialist

- * Regular assessment of growth response by a specialist in child growth at intervals: usually every 3 months during the first year.
- * If the response to treatment is satisfactory, the interval between assessments may be extended to 4-6 months.
- * Thyroid function annually or when indicated.
- * Bone age assessment annually or when indicated.
- * Assessment of pituitary status as other hormonal deficiencies may be unmasked by treatment with GH (if indicated).
- * Sex hormone replacement to induce puberty at the normal timing if indicated.
- * Examining patients with GHD secondary to an intracranial lesion for evidence of progression or recurrence of underlying disease.
- * Regular communication with the GP to update about response and developments and any change in treatment.

Aspects of care for which the GP will be responsible

- * Reporting of adverse events or significant medical conditions presented by the patient to the specialist centre.
- * Prescribing maintenance therapy. As regular administration of GH maximizes the growth response and aids compliance, repeat prescriptions should be for a minimum of one month at a time, and ideally longer (eg. 3 months).
- * Reporting of changes or additions to patient's other medication (if any).
- * Sharing in the monitoring of the child's response to treatment if the GP so wishes.

The principal method for determining the success or otherwise of GH treatment is by careful and accurate estimation of the child's growth. Whereas these methods are practised in the Growth Centre, they are not difficult to learn and should be practised routinely in the assessment of a child's growth.

Stopping GH

GH should not be stopped by default. GH should be stopped if there is a poor response to therapy (ie. <50% increment in HV in the 1st year of GH). For whatever reason. GH should be stopped at achievement of final height (HV < 2 cm/year). In addition, in children with CRI GH should be stopped at the time of renal transplantation, and not restarted until at least 1 year post-transplant, to see if catch-up growth has occurred.

Adverse Effects

GH therapy is safe and adverse effects are uncommon with recommended dosages but include these listed below.

1. Local discomfort at the site of injection has been reported and frequent subcutaneous injection into the same site may result in tissue atrophy. This can be avoided by varying the injection site.
2. Headache may be noted transiently in some patients on higher dosage regimens. Rarely benign intracranial hypertension has been reported but this can be detected by fundoscopy.
3. Oedema may be exacerbated in Turner's syndrome but is rare in other patients.

Other associations have been described but are rarely encountered in routine practice.

Hypothyroidism has been reported in 5-10% of patients undergoing treatment with GH. This may be a result of the natural history of hypopituitarism due to the associated TSH deficiency. It is essential to correct any deficiency with thyroxine if a response to GH treatment is to be achieved.

Diabetes mellitus GH exerts effects on both carbohydrate and lipid metabolism. It is both anabolic and diabetogenic and, in theory, hyperglycaemia and ketosis may occur but is rarely seen in practice. In children with existing diabetes mellitus, glycaemic control and insulin therapy may need readjustment; the induction of insulin resistance is also a rare occurrence.

Antibody development has been observed in some r-hGH treated patients, but rarely affects the clinical response to treatment.

Acute leukaemia has been reported both in untreated GHD children as well as GH treated children. Studies show that there is no increased incidence over standard population data so these reports are chance associations. The incidence in treated children is not higher even in children who have had leukaemia previously or a bone marrow transplant.

Overdose in the acute situation is likely to lead to transient hypoglycaemia followed by hyperglycaemia. The consequences of long-term treatment or overdose are unknown but carry the risk of pituitary gigantism or acromegaly. However, these occur only with higher sustained levels of GH than standard therapeutic doses.

Interaction with other medications

Corticosteroids in supra-physiological doses may interfere with the growth promoting actions of GH. Children with co-existing ACTH deficiency should have their glucocorticoid

replacement dose carefully adjusted to avoid an inhibitory effect on growth. Titration of doses should be managed by a specialist consultant.

Diabetic patients may require their glycaemic control measures reviewed (including oral hypoglycaemics and insulin therapy) to take into account the hyperglycaemic effects of GH.

References

- British National Formulary for Children (BNFC). (2005)
- National Institute for Clinical Excellence (NICE) Technology Appraisal No.42 (2002) Full guidance on the use of human growth hormone (somatropin) in children with growth failure. <http://www.nice.org.uk/pdf/HGHinChild-42-ALS.pdf>.
- National Institute for Clinical Excellence (NICE) (2002) Assessment report on clinical and cost effectiveness of growth hormone in children <http://www.nice.org.uk/pdf/AssessmentReport-Children151001.pdf>.

Glossary

ACTH: Adreno-corticotrophic hormone
BNFC: British National Formulary for Children
CRI: Chronic renal insufficiency
FH: Final height
GH: Growth hormone
GHD: Growth hormone deficiency
GP: General Practitioner
HV: Height velocity
ITT: Insulin tolerance test
PWS: Prader-Willi syndrome
SD: Standard deviation
SGA: Small for gestational age
TS: Turner syndrome

Appendix

Costs of GH; from BNFC

Genotropin (Pharmacia)

Injection, two-compartment cartridge containing powder for reconstitution, Somatropin (rbe) and diluent, net price 5.3 mg (16 unit) cartridge = £122.87, 12 mg (36 unit cartridge) = £278.20. For use with *Genotropin Pen* device (available free of charge from clinics). *For subcutaneous injection.*

MiniQuick injection, two compartment single-dose syringe containing powder for reconstitution, Somatropin (rbe) and diluent, net price 0.2 mg (0.6 unit) syringe = £4.64; 0.4 mg (1.2 unit) syringe = £9.27 0.6 mg (1.8 unit) syringe = £13.91; 0.8 mg (2.4 unit) syringe = £18.55; 1 mg (3 unit) syringe = £23.18; 1.2 mg (3.6 unit) syringe = £27.82; 1.4 mg (4.2 unit) syringe = £32.46; 1.6 mg (4.8 unit) syringe = £37.09; 1.8 mg (5.4 unit) syringe = £41.73; 2 mg (6 unit) syringe = £46.37. *For subcutaneous injection.*

Humatrope (Lilly)

Injection, powder for reconstitution, Somatropin (rbe), net price 1.33 mg (4 unit) vial (with diluent) = £30.50; 6 mg (18 unit) cartridge = £137.25; 12 mg (36 unit) cartridge = £274.50; 24 mg (72 unit) cartridge = £549.00; all supplied with diluent. *For subcutaneous or intramuscular injection, cartridges for subcutaneous injection.*

Norditropin (Novo Nordisk)

Simplex injections, Somatropin (epr) 3.3 mg (10 units)/mL, net price 1.5 mL (5 mg, 15 unit) cartridge = £115.90; 6.7 mg (20 units)/mL, 1.5 mL (10 mg, 30 unit) cartridge = £231.80; 10 mg (30 units) / mL, 1.5 mL (15 mg, 45 unit) cartridge= £347.70. For use with appropriate *NordiPen* device (available free of charge from clinics). *For subcutaneous injection.*

NutropinAQ (Ipsen)

Injection, Somatropin (rbe), net price 10 mg (30 units) 2 mL cartridge = £215.57. For use with *NutropinAq Pen* device (available free of charge from clinics). *For subcutaneous injection.*

Saizen (Serono)

Injection, powder for reconstitution, Somatropin (rmc) net price 1.33 mg (4 unit) vial (with diluent) = £29.28; 3.33 mg (10 unit) vial (with diluent) = £73.20. *For subcutaneous or intramuscular injection.*

Click easy, powder for reconstitution, Somatropin (rmc), net price 8 mg (24 unit) vial (in click easy device with diluent) = £175.68. For use with *One Click* autoinjector device or *Cool Click* needle-free device (both available free of charge from clinics). *For subcutaneous injection.*

Zomacton (Ferring)

Injection, powder for reconstitution, Somatropin (rbe), net price 4 mg (12 unit) vial (with diluent) = £81.32. For use with *ZomaJet 2* needle-free device or with *Auto-Jector* (both available free of charge from clinics) or with needles and syringes. *For subcutaneous injection.*