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National Institute for Clinical Excellence

National Institute for Clinical Excellence

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Technology Appraisal Guidance - No. 42

NHS

National Institute for Clinical Excellence

Guidance on the use of human growth hormone (somatropin) in children with growth failure

May 2002

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Ordering information
Copies of this guidance can be obtained from the NHS Response Line by telephoning 0870 1555 455 and quoting ref: N0095. A patient version of this document can be obtained by quoting ref: N0097. A bi-lingual patient leaflet is also available, ref: N0098.

Distribution of guidance

This document has been circulated to the following:

- PCT Chief Executives
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- Representative bodies for health services, professional organisations and statutory bodies, Royal Colleges

This guidance is written in the following context:
This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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Guidance on the use of human growth hormone (somatropin) in children with growth failure

1. Guidance

1.1 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.

1.2. 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.

1.3. 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 therapy has been reduced to minimum.

1.4. GH treatment is recommended for children with Prader-Willi syndrome.

1.5. 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.

1.6. GH treatment should be re-evaluated and normally discontinued if there is a poor response to treatment, defined as an 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 normally be 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.

1.7. 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 be continued until re-evaluation 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.

1.8. 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.

1.9. 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.

This section (Section 1) constitutes the Institute's guidance on the use of human growth hormone (somatropin) in children with growth failure. The remainder of the document is structured in the following way:

A bi-lingual summary is available from our website at www.nice.org.uk or by telephoning 0870 1555 455 and quoting the reference number N0096.

Mae crynodeb ar gael yn Gymraeg ac yn Saesneg ar ein gwefan yn www.nice.org.uk neu drwy ffonio 0870 1555 455 gan ddyfynnu cyfeirnod N0096.

2 Clinical need and practice

2.1 Growth hormone (GH), also known as somatropin, is a hormone produced by the anterior pituitary gland. GH is essential for normal growth in children and acts by increasing growth, both by a direct action on the growth plates and via the production of insulin-like growth factors (especially IGF-1) mainly in the liver. GH also has important effects on protein, lipid and carbohydrate metabolism, not only during childhood, but also throughout adult life. Among children who are of very short stature (i.e. at least 3 standard deviations below the population mean), 25% have GH deficiency.

2.2. GH deficiency may occur as an isolated hormonal deficiency or in combination with multiple pituitary hormone deficiency (MPHD) as a result of hypopituitarism, tumours in the central nervous system, cranial irradiation or other organic causes. Idiopathic growth hormone deficiency (IGHD) is the most common form, accounting for approximately 50–70% of cases.

2.3. Growth failure is a prominent feature in children with chronic renal insufficiency (CRI) and Turner syndrome (TS). Growth failure associated with CRI and TS is thought to be multifactorial, with one of the factors being reduced sensitivity to GH, rather than decreased GH levels. Therefore, supra-physiological doses of GH are required for treatment in children with these conditions. Children with Prader-Willi syndrome (PWS) are considered to have a hypothalamic disorder, and thus GH therapy is intended to replace physiological levels of GH.

2.4. The estimated annual incidence and prevalence of each condition is shown in Table 1.

Condition	Annual incidence (Age < 16 years)		Prevalence (Age < 16 years)	
	England	Wales	England	Wales
GH deficiency	120	7	2726	162
TS	84–196	5–11	1341–3130	75–175
CRI	86	5	607	36
PWS	32	2	512	32

2.5. GH deficiency is primarily a clinical diagnosis, supported by auxological (measurements of height), biochemical and radiological findings. The diagnosis is usually confirmed by appropriate GH provocation tests, which evaluate the GH reserve of the children. In suspected isolated GH deficiency, two GH provocation tests (sequentially or on separate days) with an evaluation of other aspects of pituitary function are required. However in children with defined CNS pathology, history of irradiation, MPHD or a genetic defect affecting the GH axis, one GH test will suffice.

2.6. The definition of a normal response is still rather arbitrary as there is a continuous spectrum of GH secretion in childhood. In a child with clinical criteria for GH deficiency, peak GH concentrations below 20 mU/litre have traditionally been used to support the diagnosis. However this value will vary depending on the GH immunoassay used and needs to be revised downwards when using newer monoclonal-based assays and recombinant GH reference preparations.

2.7. Magnetic resonance imaging of the brain with particular attention to the hypothalamic–pituitary region should be carried out in any child diagnosed as having GH deficiency, to exclude the possibility of a tumour.

2.8. GH therapy is currently the mainstay treatment to correct growth failure for children with GH deficiency and with TS. In these groups of children, there are no other active treatment options to increase stature. Oxandrolone may be added to GH treatment regimens for treatment of girls with TS. In the UK, conservative management strategies for CRI include diet guidance and nutritional supplementation.

2.9. The aim of treatment in PWS is to improve the body composition as well as promoting growth, as most children with PWS are obese. Dietary management and appetite suppressants have been tried with very limited success, partly because of the behavioural problems associated with this condition.

3 The technology

3.1 Biosynthetic human growth hormone (somatropin) is available as five preparations on the UK market: Genotropin, Humatrope, Norditropin, Saizen and Zomacton. Each product is produced by recombinant DNA technology and has a sequence identical to that of human GH. The licensed indications are:

- long-term treatment of children who have growth failure due to inadequate secretion of normal endogenous GH
- treatment of short stature in children with TS, confirmed by chromosome analysis
- treatment of growth retardation in pre-pubertal children with CRI (all but Zomacton)
- for improvement of growth and body composition of patients with PWS, confirmed by appropriate genetic testing (Genotropin only).

3.2. The recommended dose varies according to the condition being treated: 0.025–0.035 mg/kg/day for GH deficiency, 0.045–0.050 mg/kg/day for TS and CRI, and 0.035 mg/kg/day for PWS. GH is self-administered at home, as a subcutaneous injection, 6–7 times a week.

3.3. GH has a good safety profile based on many thousand patient years of follow-up. Side effects of GH therapy are rare, but may include headache, visual problems, nausea and vomiting, fluid retention (peripheral oedema), arthralgia, myalgia, paraesthesia, antibody formation, hypothyroidism and reactions at the injection site. Particular attention should be paid to treating children with risk factors associated with diabetes mellitus, slipped capital epiphyses, idiopathic intracranial hypertension and malignancies. GH therapy is contraindicated in cases of tumour activity, in seriously ill children or for growth promotion in children with closed epiphyses.

3.4. The cost of drug treatment depends on the dose, which is determined by the weight/size of the patient, as well as the condition to be treated. The BNF prices (March 2002 BNF excluding VAT) are £21.86 per mg for Zomacton, £22.76 per mg for Genotropin, £22.87 per mg for Humatrope and Saizen, and £23.42 per mg for Norditropin.

4 Evidence

4.1 Clinical effectiveness

Growth hormone deficiency

4.1.1 One randomised controlled trial (RCT) and two non-RCTs were identified. Results from the published RCT (n = 49) show that GH therapy is effective in promoting growth in children with GH deficiency. Height standard deviation scores (HtSDS) and growth velocity (GV) in children on GH treatment (15 U/m2/week) were significantly improved in comparison with children receiving no treatment over the study period of 1 year (HtSDS: +1.1 in the GH group versus +0.3 in the placebo group, $p < 0.05$; GV: 4.75 cm versus 1.4 cm, $p < 0.05$). The quality of reporting for this RCT was poor; it was not described as a double-blind study and the randomisation method was not reported.

4.1.2. The results of two retrospective single cohort studies, which evaluated height before and after treatment in children with IGHD, showed improvements in the final height of approximately 1.3–1.6 SD from pre-treatment measures. The durations of these studies were 4.5 and 8.1 years. Using current adult height norms and assuming that untreated children would maintain their pre-treatment HtSDS at final height, the height gain due to GH treatment would be approximately 8.7–10.7 cm for boys and 7.7–9.5 cm for girls.

Turner syndrome

4.1.3 Four RCTs (three published and one provided by the manufacturer in confidence) and four non-RCTs were identified. One of the RCTs presented final height data in 69 patients and reported short-term psychological outcomes of 48 patients in a separate publication. Another reported short-term growth outcome in 35 patients. The third published trial reported short-term cognitive outcomes (n = 40). All of these RCTs lacked information about randomisation and only one was double-blind.

4.1.4. One of the published RCTs showed that GH was effective in children with TS, increasing short-term GV by approximately 2.8 cm at 1 year. Girls treated with GH were approximately 5 cm taller than untreated girls in the one RCT that reported final height from a subset of the original sample of patients. In the RCT that was provided by the manufacturer, the short-term growth over 18 months was 2.4–2.8 cm/year greater in treated than in untreated girls.

4.1.5. Four non-randomised studies, with sample size ranging from 31 to 123, reported final height in children with TS. These studies included treated and untreated patients, but lacked appropriate sampling and there were problems with equivalence of comparison groups. Results from these studies have shown that the girls treated with GH were approximately 4–5 cm taller at final height than untreated girls. One study reported no statistically significant improvement in final height in the GH-treated group (2.1 cm), and another reported a final height gain of approximately 7 cm. There was considerable variation between patients in response to GH treatment.

Chronic renal insufficiency

4.1.6. Five RCTs met the inclusion criteria. Three trials included patients who were in chronic renal failure, but who had not received a renal allograft (n = 16, n = 44 and n = 125), whereas two other RCTs included patients who had received kidney transplants (n = 11 and n = 203). Two non-randomised studies were also considered because no final height data were available in the context of an RCT.

4.1.7. The available evidence from RCTs suggests that GH is effective in patients with CRI, increasing short-term height changes of approximately 0.5–0.8 SD over 1 year and 1.3 SD over 2 years. GV improved by approximately 3–4 cm/year in the first year and by approximately 2.3 cm in the second year of a 2-year study. In the shortest

studies (with duration of 6 months), GV was greater (by approximately 2–4 cm/6 months) in children receiving GH than in those receiving placebo. Results were similar whether patients were treated before or after receiving a kidney transplant.

4.1.8. Two non-randomised studies (one prospective and one retrospective), involving 31 and 88 CRI or post-transplantation patients, compared the final height in GH-treated and untreated groups. In the prospective study the groups were not equivalent at baseline, and in the other study there are concerns about the sampling methods used. In one study, boys treated with GH were only approximately 3 cm taller than untreated boys, but in the other study boys treated with GH were approximately 9 cm taller than untreated boys. Girls treated with GH were approximately 4 cm taller than untreated girls in one study and approximately 8 cm taller than untreated girls in the other study. The study with the greater final height gains reported medians, involved smaller numbers of patients, and used historical controls. However, in the other study the treatment and control groups were self-selected and the control participants were taller at baseline, and so this study is likely to have underestimated the effects of treatment.

4.1.9. A recent Cochrane review concluded that 1 year of GH treatment (28IU/m^2/week) in children with CRI results in a 4-cm/year increase in GV above that of untreated controls. However, it is not certain whether this increase in GV will result in an increase in final adult height.

Prader-Willi syndrome

4.1.10 Three RCTs compared GH treatment with no treatment in a total of 97 (n = 54, n = 27 and n = 16) children with PWS. The trials were all 1 year in duration. One single cohort study reported final height in 16 treated children. The quality of the RCTs was poor and the non-RCT was reported only as an abstract.

4.1.11. One-year growth was greater in children receiving GH, resulting in treated children being approximately 1 SD taller than the untreated children. Short-term GV was also substantially greater in the treated than the untreated children. Body composition was also improved over the short term in children treated with GH. They had 7–8% less fat and approximately 4 kg more lean body mass than untreated children. Children treated with GH did not differ from untreated children across a range of behaviours and psychological symptoms. There were small improvements from baseline within a GH-treated group in obsessional thoughts and skin picking.

4.1.12. The non-RCT reported final height of 170 cm in boys and 159 cm in girls. These heights are well within the normal range. Presuming a treatment effect based on the change in SD from the start to end of treatment, there was a change of 1.64 SD. Converting this SD change to centimetres in adult height, this corresponds to treated boys being approximately 11 cm taller than untreated boys would be predicted to be, and treated girls being approximately 9.8 cm taller than untreated girls would be. These results should, however, be treated with caution as there was no control group, the number of participants was small, it is not known how representative the participants of the study were of the population of patients with PWS, and certain assumptions have been made in estimating a treatment effect.

4.2 Cost effectiveness

4.2.1 The Assessment Report, prepared by the Wessex Institute for Health Research and Development, included a cost-effectiveness analysis and reported the incremental cost-effectiveness ratio (ICER) as an expected incremental mean cost per centimetre of final height gained for children with GH deficiency, CRI, TS or PWS, and expected (discounted) incremental mean cost per unit HtSDS improvement at 1 year for children with PWS. This analysis suggests that under base-case conditions the cost per centimetre gained in final height is around £6000 for GH deficiency, from £15,800 to £17,300 for TS, from £7400 to £24,100 for CRI, and possibly in the region of £7030 for PWS (2000 prices).

4.2.2. Four models were submitted to the Institute by manufacturers; two estimated cost-utility of GH use in children, one provided cost effectiveness in the form of cost per centimetre gained and the other calculated cost effectiveness in terms of cost per normalised year gained. One manufacturer's submission included a cost-minimisation analysis.

4.2.3. One manufacturer's model estimated the ICER in terms of cost per centimetre gained as £3600 in boys with GH deficiency, £4264 in girls with GH deficiency and between £6395 and £9215 in girls with TS. Another model estimated the incremental cost per normalised height year as £2118–£2156 for GH deficiency, £3560–£4025 for TS and £1238–£2339 for CRI. Normalised height was defined as less than 2 SDs lower than the population mean.

4.2.4. Two manufacturers adopted the methodology used in a 1996 Wessex DEC report to generate utility estimates in their models. The 1996 report was based on unsubstantiated estimates of utility gain as no primary studies were available to inform the relationship between the degree of height gain and psychological benefits gained from treatment. The ICERs published in the 1996 report were £5700 to £20,800 per quality-adjusted life year (QALY) for GH deficiency, and £11,400 to £41,700 per QALY for TS and CRI. The ICERs estimated by the manufacturers' models were between £5500 and £9000 per QALY gained in GH deficiency, between £10,500 and £18,000 for TS, and between £5000 and £11,000 for CRI. These models also do not use primary data, but base likely utility gains on similarly unsubstantiated broad estimates, and therefore should be treated with caution.

4.3 Consideration

4.3.1 The Committee reviewed the evidence on both the clinical effectiveness and the cost effectiveness of GH treatment in children with GRD, TS, CRI or PWS, having considered evidence from children with these diseases via their carers, patient/carer groups and clinical experts on the nature of the condition and the value placed by users on the effects of GH treatment. It was also mindful of the need to ensure that its advice took account of the efficient use of NHS resources.

4.3.2. In its consideration the Committee recognised the value of research evidence from both RCT and observational sources, including the KIMS/KIGS (Pharmacia International Metabolic and Growth Databases) and similar databases.

4.3.3. The Committee considered that although it had reservations about the calculation of the likely utility gains, the underlying assumptions relating to the level of gain were reasonable. This was supported by the cost-effectiveness analysis on height gain alone.

4.3.4. The Committee concluded that the utility gain from the height gain in treatment of GH deficiency, TS, CRI or PWS was a worthwhile gain for the resource, given its lifelong value and the psychological importance to the child.

5 Implications for the NHS

5.1 The mean annual cost of treatment was estimated to be £6103 for a child with GH deficiency, £10,126 for a child with TS, £11,132 for a child with CRI, and £9840 for a child with PWS. These estimated figures were derived from the economic analysis included in the Assessment Report and based on the annual treatment costs of a 30-kg child.

5.2. According to a published UK audit of GH prescriptions performed in 1998, it is estimated that there are over 1600 children with GH deficiency, TS or CRI in England and Wales who are currently receiving GH treatment, incurring costs of around £12 million to the NHS annually. However, there are estimated to be around another 1740 children with GH deficiency, 955–2750 children with TS and 330 children with CRI in England and Wales who may be eligible for, but are not currently receiving, GH treatment. Treating those patients would cost the NHS an additional £24 to £42 million per annum.

5.3. The number of children with PWS who are currently receiving GH treatment is unknown. The cost of treating all eligible PWS patients (around 500) would be around £5 million per annum, but only a proportion of this cost would be incurred, depending on the number of the PWS patients who currently receive GH treatment.

6 Further research

6.1 Further good quality studies are needed to clarify:

- the impact of GH treatment on quality of life, including the description of the extent of any potential benefits in the form of meaningful utility scores
- the optimal dosing strategies in the management of patients in transition from paediatric to adult care
- the optimal starting age and length of GH treatment for girls with TS, and the optimal timing of oestrogen treatment along with GH
- the optimal treatment strategies of GH treatment for children with PWS.

7 Implementation

7.1 Those providing care for children with growth failure should review policies and practices regarding the prescription of human growth hormone in children to take account of the guidance set out in Section 1.

7.2. Local guidelines or care pathways on children with growth failure should incorporate the guidance set out in Section 1.

7.3. To measure compliance locally with the guidance set out in Section 1, the following criteria should be used. Technical details on the criteria are given in Appendix D.

- GH treatment is prescribed for children with the following conditions: GH deficiency, TS, CRI or PWS.

- For a child with GH deficiency, the diagnosis is made by auxological, biochemical and radiological findings and is confirmed by two GH provocation tests, with an evaluation of other aspects of pituitary function, except for children with defined CNS pathology, history of irradiation, MPHD or a genetic defect affecting the GH axis, who may need one GH test only.

- For a pre-pubertal child with CRI, treatment should be initiated only if nutritional status has been optimised, metabolic abnormalities have been optimised, and steroid therapy has been reduced to a minimum.

- GH treatment is initiated and monitored only by a paediatrician with special expertise in the management of GH disorders.

- GH treatment is re-evaluated against expected growth. Re-evaluation includes taking account of persistent and uncorrectable problems with adherence to treatment with the therapy and in PWS, body composition.

- GH treatment is discontinued in the following circumstances:

  - the child has a poor response to treatment

  - a child with CRI has a transplantation

  - the child attains final height.

- The decision to stop treatment is made by the paediatrician with special expertise in the management of GH disorders in consultation with the patient and carers or therapy is continued until re-evaluation by an adult endocrinologist has been undertaken.

7.4. Local clinical audits on the care of children who are prescribed GH could also include criteria on the local shared-care protocol for continuation of treatment for these children and on the management of children to adult GH replacement.

8 Related guidance

8.1 The Institute expects to issue guidance on the use of GH treatment in adult patients in summer 2002.

9 Review of guidance

9.1 This advice will be reviewed in the light of new evidence in June 2005.

Andrew Dillon
Chief Executive

May 2002

APPENDIX A

Appraisal Committee members

The Appraisal Committee is a statutory committee whose members sit for 3 years. Two meetings are held per month and the majority of members attend one or the other. Declared interests may also exclude a member from individual technology appraisals. The Committee are supplemented by technology specific experts as indicated in Appendix B.

Professor R. L. Akehurst
Dean, School of Health Related Research
Sheffield University

Professor David Barnett (Chairman)
Professor of Clinical Pharmacology
University of Leicester

Professor Sir Colin Berry
Professor of Morbid Anatomy
St Bartholomew's and Royal London School of Medicine

Dr Sheila Bird
MRC Biostatistics Unit,
Cambridge

Professor Martin Buxton
Director of Health Economics Research Group
Brunel University

Dr Karl Claxton
Lecturer in Economics
University of York

Professor Sarah Cowley
Professor of Community Practice Development
Kings College, London

Professor Nicky Cullum
Reader in Health Studies
Department of Health Sciences
University of York

Mr Chris Evennett
Chief Executive
Mid-Hampshire Primary Care Group

Professor Terry Feest
Clinical Director and Consultant Nephrologist
Richard Bright Renal Unit and
Chairman of the UK Renal Registry

Ms Jean Gaffin
Formerly Executive Director
National Council for Hospice and Specialist Palliative Care Service

Mrs Sue Gallagher
Chief Executive
Merton, Sutton and Wandsworth Health Authority

Dr Trevor Gibbs
Head, Global Clinical Safety & Pharmacovigilance
GlaxoSmithKline

Mr John Goulston
Director of Finance
The Royal Free Hampstead NHS Trust

Professor Philip Home
Professor of Diabetes Medicine
University of Newcastle

Dr Terry John
General Practitioner
The Firs, London

Dr Diane Ketley
Research into Practice Programme Leader
NHS Modernisation Agency

Dr Mayur Lakhani
General Practitioner, Highgate Surgery, Leicester and Lecturer,
University of Leicester

Mr M Mughal
Consultant Surgeon
Chorley and South Ribble NHS Trust

Mr James Partridge
Chief Executive
Changing Faces

Professor Philip Routledge
Professor of Clinical Pharmacology
University of Wales College of Medicine

Professor Andrew Stevens (Vice Chairman)
Professor of Public Health
University of Birmingham

Dr Cathryn Thomas
General Practitioner/Senior Lecturer
Department of Primary Care & General Practice
University of Birmingham

APPENDIX B

Sources of evidence

The following documentation and opinion was made available to the Committee:

a. Assessment Report:

- prepared by the Wessex Institute for Health Research and Development, University of Southampton: *The Clinical and Cost Effectiveness of Growth Hormone in Children*, October 2001

b. Manufacturer/sponsor submissions :

- Eli Lilly
- Ferring
- Novo Nordisk
- Pharmacia

c. Professional/specialist group submissions:

- Department of Diabetes, Endocrinology and General Medicine, The Guy's, King's College and St Thomas' Hospitals Medical and Dental School
- Royal College of Physicians and the Society for Endocrinology
- The British Society for Paediatric Endocrinology and Diabetes and The Royal College of Paediatrics and Child Health

d. Patient group submissions:

- Child Growth Foundation
- Pituitary Foundation
- Prader-Willi Syndrome Association (UK)
- Restricted Growth Association
- Turner Syndrome Support Society

e. External expert and patient advocate perspectives:

- Dr Gary Butler, Consultant Paediatric Endocrinologist, Leeds General Infirmary and British Society for Paediatric Endocrinology and Diabetes
- Ms Patsy Perrin and Dr Janet Harbour, Pituitary Foundation
- Dr D A Price, Senior Lecturer in Child Health, Royal Manchester Children's Hospital and on behalf of the Turner Syndrome Support Society
- Mrs Arlene Smyth, Turner Syndrome Support Society
- Professor M C Sheppard, Professor of Medicine and Head of Division, Queen Elizabeth Hospital, Birmingham

APPENDIX C

Patient/carer information

Guidance on the use of human growth hormone (somatropin) in children with growth failure

The patient information in this appendix has been designed to support the production of your own information leaflets. You can download it from our website at www.nice.org.uk where it is available in English and Welsh. If you would like printed copies of the leaflets please ring the NHS Response Line on 0870 1555 455 and quote reference number N0097 for the English patient leaflet and N0098 for the bi-lingual patient leaflet.

What is NICE guidance?

The National Institute for Clinical Excellence (NICE) is part of the NHS. It produces guidance on the use of medicines, medical equipment and clinical procedures for people working in the NHS in England and Wales, and for patients and their carers.

To produce this guidance, NICE looks at how well the medicine, equipment or procedure works and also how well it works in relation to how much it costs. This process is called an appraisal. The appraisal process involves the manufacturer of the medicine or equipment for which guidance is being produced, and the organisations that represent the healthcare professionals, patients and carers who will be affected by the guidance. Each appraisal takes about 12 months to complete.

What is this guidance about?

NICE has looked at the evidence available on the use of biosynthesised human growth hormone, which is also called somatropin, in children who are not growing normally – they have 'growth failure'.

What is human growth hormone?

Human growth hormone is a hormone produced by the pituitary, which is a small gland inside the head. Growth hormone is essential for growth in children. It also has important effects on how the body deals with protein, fats and carbohydrates, not only during childhood, but also throughout adult life.

Some children do not produce enough growth hormone or do not respond as expected to growth hormone, and so they do not grow as they should. They are much shorter than would be expected for their age.

Children who have 'growth hormone deficiency' do not have enough growth hormone. Sometimes it is known what is causing the lack of growth hormone – for example, there is a problem with the pituitary gland. But for 5 to 7 out of every 10 children with growth hormone deficiency, the cause is not known.

Failure to grow normally is also a key feature of several other medical conditions. The most common of these are reduction in kidney function (known as 'chronic renal insufficiency') and conditons known as Turner syndrome (which only affects girls) and Prader-Willi syndrome.

What is somatropin and how does it work?

Somatropin is biosynthetic, or laboratory produced, human growth hormone. It is the same chemically as the growth hormone produced by the body. Somatropin is made by a process known as genetic engineering.

Somatropin is given to increase growth in children who have growth hormone deficiency, Turner syndrome, chronic renal insufficiency or Prader-Willi syndrome. For children with Prader-Willi syndrome, growth hormone treatment is also given to improve body composition – children with Prader-Willi syndrome often have too much body fat and growth hormone can help to correct this.

What has NICE recommended?

NICE has made the following recommendations about the use of human growth hormone (somatropin) to treat children with growth hormone deficiency, Turner syndrome, chronic renal insufficiency or Prader-Willi syndrome. Note that at the time this guidance was issued, somatropin was not licensed to treat children who are not growing despite normal levels of growth hormone because of another unknown reason, and so this guidance does not deal with that use of somatropin.

- Human growth hormone (somatropin) treatment is recommended for children who have growth hormone deficiency. To help diagnose growth hormone deficiency the doctor should take measurements of height and look at the results of radiological investigations and tests to measure the amount of GH in the child's blood.

- Growth hormone treatment is recommended for girls with Turner syndrome. For the treatment to work as well as possible, they should be diagnosed and start treatment at the earliest age possible and they should be given oestrogen treatment at the right time to stimulate puberty.

- Growth hormone treatment is recommended for children with chronic renal insufficiency who have not yet reached puberty. Before giving growth hormone treatment the doctor should make sure that the child's nutrition (food intake) and metabolism (chemical processes inside the body) are as good as possible. Treatment with steroids should be at the lowest level possible.

- Growth hormone treatment is recommended for treating children with Prader-Willi syndrome.

- A paediatrician (a doctor who specialises in treating children) who is an expert in treating children with a growth hormone disorder should always be responsible for starting and checking the progress of growth hormone treatment.

- Usually, growth hormone treatment should be stopped after the first year if the extra height gain is not at least half the height gain in the year before treatment began. For a child who continues treatment after the first year, treatment should be stopped, after discussion with the child and carer, when the expected final height has nearly been reached, or when the child has grown less than 2 cm in 1 year. Alternatively, treatment should be continued until the person can be seen by a doctor who specialises in treating adults with a hormone disorder (an adult endocrinologist).

- The doctor who is treating a child with Prader-Willi syndrome should consider the amount of fat in the body as well as height when considering when to stop treatment with growth hormone. This is because children with Prader-Willi syndrome often have too much body fat.

- The doctor should consider stopping treatment with growth hormone before a child has reached final height if the child is not taking the treatment regularly.

- If a child with chronic renal insufficiency has a kidney transplant, growth hormone treatment should be stopped. It should not usually be started again until at least 1 year after the transplant. This is so that doctors can see whether the child's growth catches up after the transplant.

What should I do?

If you are child with a growth hormone disorder, you can discuss this guidance with the doctor at your next hospital appointment. If you are the parent or carer of a child with a growth hormone disorder you should discuss this guidance with the doctor at the next hospital appointment.

Will this guidance be reviewed?

Yes. This guidance will be reviewed in June 2005.

Further information

Further information about NICE and the full guidance on the use of human growth hormone (somatropin) in children with growth failure that has been issued to the NHS are available on the NICE website at www.nice.org.uk. The full guidance can also be requested by calling 0870 1555 455 and quoting reference number N0095.

If you have access to the Internet and would like to find out more about growth hormone disorders and how they are treated, visit the NHS Direct website: www.nhsdirect.nhs.uk. If you would like to speak to NHS Direct please call them on 08 45 46 47.

APPENDIX D

Technical detail on the criteria for audit of the use of human growth hormone in children with growth failure

Possible objectives for an audit

An audit on the appropriateness of prescription of growth hormone (GH) treatment for children could be carried out to ensure that:

- GH treatment is prescribed for children with GH deficiency, Turner syndrome (TS), chronic renal insufficiency (CRI) or Prader-Willi syndrome (PWS)
- GH treatment is continued only as long as it provides benefit
- GH treatment is initiated, monitored and discontinued by an appropriate paediatrician in consultation with the patient and carers.

Children to be included in an audit and time period for selection

All children receiving GH treatment over the past year. Alternatively, an audit could be constructed to identify children seen in the past year, for example, with GHD, TS, PWS or CRI to determine if GH therapy was considered as part of the management of their conditions.

Measures to be used as a basis for an audit

The measures that can be used in an audit of the appropriateness of prescription of GH treatment are as follow overleaf:

Measures to be used as a basis for the audit

Criterion	Standard
1. GH is prescribed for one of the following conditions: a. GH deficiency or b. TS or c. PWS or d. CRI	100% of children receiving GH
2. GH deficiency is diagnosed by auxological, biochemical and radiological findings and is confirmed by 2 GH provocation tests with an evaluation of other aspects of pituitary function	100% of children receiving GH for GH deficiency
3. A child with CRI is prescribed GH only if all of the following have been established: a. Nutritional status has been optimised and b. Metabolic abnormalities have been optimised and c. Steroid therapy has been reduced to minimum	100% of children with CRI who are receiving GH
4. An appropriate paediatrician carries out the following: a. Initiates GH treatment and b. Monitors GH treatment and c. Discontinues treatment in consultation with the patient and carers	100% of children receiving GH for 4a, 4b and 4c
5. GH treatment is re-evaluated	100% of children receiving GH
6. Prescription of GH is discontinued when any of the following occur: a The child has a poor response to treatment or b A child with CRI has a transplant or c The child attains final height	100% of children for whom GH is prescribed

Calculation of compliance with the measure

Compliance with each measure described in the table is calculated as follows:

$$\frac{\text{Number of children whose care is consistent with the } \textbf{Criterion} \textit{ plus} \text{ number of children who meet any } \textbf{Exception} \text{ listed}}{\text{Number of children to whom the } \textbf{Measure applies}} \times \mathbf{100}$$

The measures that can be used in an audit of the appropriateness of prescription of GH treatment are as follow:

Exception	Definition of Terms
None	See 2 for evidence supporting GH deficiency
A child with any of the following may have 1 GH test only: A. Defined CNS pathology B. History of irradiation C. Multiple pituitary hormone deficiency (MPHD) D. A genetic defect affecting the GH axis	Specialists should agree locally on diagnostic findings and on definitions of the exceptions for audit purposes
None	Child = pre-pubertal or pubertal with documented growth failure. Specialists should agree locally on definitions of 3a-c for audit purposes
For 4a and 4b, none For 4c, for a child with GH disorder who has reached final height, GH is continued until the child is evaluated by an adult endocrinologist	An appropriate paediatrician = paediatrician with special expertise in the management of children with GH disorders. Specialists should agree locally on what constitutes monitoring. Specialists should agree on how the decision to stop treatment with GH is documented for audit purposes. If a shared-care arrangement is in place, specialists should agree locally on what constitutes shared care with GPs and what evidence is needed to confirm that a shared-care protocol is being followed for audit purposes
None	Re-evaluation is against expected growth and growth velocity based on standard growth charts. It includes taking account of persistent and uncorrectable problems with adherence to treatment and in PWS, body composition. Specialists should agree locally on how re-evaluation is documented for audit purposes
A. For a child with CRI, GH may be re-started after 1 year post-transplantation B. For a child with GH deficiency who has reached final height, GH may be continued until the individual is evaluated by an adult endocrinologist	Poor response to treatment = increase in growth (height) velocity of less than 50% of the previously documented growth (height) velocity (where growth has been subnormal) in the first year of treatment Final height = <2 cm growth in 1 year.

Clinicians should review the findings of measurement, identify if practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.