BACKGROUND

Growth Hormone (GH) is available as a biosynthetic and biosimilar growth hormone with a sequence identical to human pituitary GH. Since the withdrawal of cadaveric (pituitary) GH in 1985 after the association with a slow virus infection was appreciated (Jacob Creutzfeld Disease), biosynthetic and biosimilar GHs are the only preparations available in the United Kingdom. Biosynthetic GHs are made from either E.Coli bacteria (Eli Lilly, Ferring, Ipsen, Novo Nordisk and Pfizer) or a mammalian cell line (Serono), which act as hosts to recombinant plasmids containing the human GH gene. Biosimilar GHs (Sandoz) are made with similar processes and in general should show similar physicochemical properties, along with bio equivalence, to the established biosynthetic preparations. Treatment with somatropin should always be initiated and monitored by a paediatrician with specialist expertise in managing growth hormone disorders in children. The choice of product should be made on an individual basis after informed discussion between the responsible clinician and the patient and/or their carer about the advantages and disadvantages of the products available, taking into consideration therapeutic need and the likelihood of adherence to treatment.

1. A patient with confirmed GH deficiency and in an otherwise stable condition does not require frequent hospital supervision and will be reviewed in the endocrine clinic 2-3 times a year.

2. Biosynthetic GH has a good safety record and monitoring of response more frequently than every 3-6 months is not required. Dose adjustments may be required annually, and will be based on changes in height and weight and IGF 1 levels.

3. GH therapy is expensive and continuation has to be justified by objective evidence of accelerated growth rate and improvement of predicted final height. The Endocrinology department has facilities for this assessment and will provide regular updates on patients’ response to treatment to GPs.

4. A minority of candidates for GH therapy have had, or continue to have complex health disorders requiring specialist management e.g. children with a brain tumour, complex midline defects and MPHD. GP and specialist must discuss each case individually in order to agree on a treatment and shared care strategy and agree as to when treatment with GH is most appropriate e.g. when the patient is in remission.

RESPONSIBILITIES

Consultant/Specialist Responsibilities

1. To confirm that proposed therapy is not contra-indicated because of concurrent therapy for other conditions the patient may have.

2. To ensure that the patient has been stabilised on any other drug therapy.

3. To provide GP and family with a written list of all current drug treatment.

4. To discuss the potential benefits, side effects and stopping criteria of treatment with the patient and carer.

5. To review the patient’s growth and general condition at 3-6 monthly intervals. To include accurate height and weight measurements and bone age assessment as indicated, and determination of pubertal status. To undertake provocation testing and MRI as indicated, in order to make diagnosis. All patients on growth hormone treatment require plasma IGF-1 concentrations to be monitored at 4-6 monthly intervals in adults and yearly in children. To provide the GP with information of the diagnosis and indication for GH therapy, outlining dosage, cost and product information. Products should be prescribed by brand to avoid confusion.

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AUTHOR: Mary Tompkins, Assistant Director (Evidence Based Medicine and Medicines Strategy)
6. To request of GP that necessary arrangements are made locally and fed back to the specialist centre to identify any possible barriers to treatment being commenced.
7. To provide the patient/carer with up to date information on growth hormone treatment and products available in the UK, in order for patient to decide on preferred method of administration.
8. To provide the patient/carer with a patient held record for monitoring and to alert other relevant clinical staff to the treatment they are receiving.
9. To seek funding approval (using the agreed form) from the patient’s primary care trust (PCT) for commencement of GH treatment and at annual intervals thereafter. The GP to be copied into this request.
10. When GH is not licensed for a particular indication, to make an application for funding via the commissioning body’s Individual Funding Request panel.
11. To report adverse effects to the CSM. If the indication is unlicensed, all adverse effects should be reported even if a causal relationship is not known or if the adverse effect is already known about.
12. To review GH dosage guided by height velocity, weight/surface area, pubertal stage and plasma IGF-1 concentration.
13. To advise the GP as to the continued justification for GH therapy.
14. To review associated drug therapy.
15. To teach and monitor injection techniques
16. To ensure clear arrangements are in place for back up, advice and support, e.g. out of hours and/or when the specialist initiating treatment is not available.
17. To decide on the timing of cessation of treatment, reassessment, and transition to adult care for adult GH therapy.
18. To advise re GH usage, safe storage and disposal of injection equipment and requirements for long distance travel.
19. To monitor outcomes as follows:
   ○ Growth velocity must be at least 150% of baseline level for the first 3 consecutive years.

### Short, Medium and Long Term End Points of Growth Hormone Therapy in GHD Children

<table>
<thead>
<tr>
<th>End Point</th>
<th>Rationale</th>
<th>Measure</th>
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<tr>
<td><strong>Short Term</strong></td>
<td></td>
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</tr>
<tr>
<td>1. Growth acceleration</td>
<td>1. Assess response</td>
<td>1. Growth velocity must be at least 150% of baseline level for the first 3 consecutive years.</td>
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<tr>
<td>mass</td>
<td>3. Optimise Therapy</td>
<td>3. IGF-1 and growth</td>
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<tr>
<td>3. Correct Dose</td>
<td>4. Possible Raised Intracranial</td>
<td>4. Fundoscopy</td>
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<tr>
<td>Vision and headaches</td>
<td>Pressure</td>
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<tr>
<td>5. Assessment of limp</td>
<td>5. Slipped femoral epiphysis</td>
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<td><strong>Medium Term</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Bone maturation</td>
<td>1. Rate of skeletal maturation</td>
<td>1. 1-2 Yearly Bone age</td>
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<tr>
<td>2. Pubertal Status</td>
<td>2. Early puberty or rapid</td>
<td>2. 6 monthly Tanner staging</td>
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<tr>
<td></td>
<td>progression</td>
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<tr>
<td>3. Correct Dose</td>
<td>3. Optimise therapy</td>
<td>3. IGF-1 and growth response. Return to Target Height within 6 years of therapy</td>
</tr>
<tr>
<td><strong>Long Term</strong></td>
<td></td>
<td></td>
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<tr>
<td>4. Thyroid status</td>
<td>4. Altered status or evolving</td>
<td>4. Yearly thyroid function tests</td>
</tr>
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<td></td>
<td>endocrinopathy</td>
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</tbody>
</table>
5. Other hormones
6. Metabolic Status

**Long Term**
1. Growth
2. Bone mineralisation
3. Malignancy Risk
4. Cardiovascular risk

5. Evolving endocrinopathy
6. Insulin insensitivity

5. Gonadotroph and corticotroph function
6. Fasting glucose and insulin

**General Practitioner/ Local Paediatrician/ Prescriber responsibilities**
1. Monitor patient’s overall health and well-being.
2. Ensure that the specialist’s request to commence GH treatment has been approved by the local commissioning organisation’s prescribing advisor.
3. Once local consideration of treatment has occurred, to feedback to the endocrine consultant where there are concerns regarding the prescribing of GH.
4. To prescribe GH therapy by brand name for **licensed indications** as part of a Shared Care agreement, using the specific prescribing information provided by the specialist. At this point, to ensure that patients are aware of who is undertaking the monitoring and for how long GH will be prescribed before a review is received.
5. Reporting adverse effects of therapy to the specialist or deputy.
6. To ensure that the family knows what significant adverse effects to report urgently and to whom they should report.
7. To monitor usage of GH, safe storage and disposal of injection equipment.
8. To seek specialist advice promptly if there is any clinical suspicion of loss of efficacy.
9. To stop treatment on advice of specialist, or immediately if intolerable side effects occur provided it is safer to do so than to continue treatment.

**Primary Care Trust / GP Commissioning Consortium**
1. To provide funding approval for the commencement of GH, and at review dates.
2. To support GPs to make the decision whether or not to accept clinical responsibility for prescribing.

**Patient / Parents / Carers’ role**
1. To ensure they have clear understanding of the treatment.
2. To give the growth hormone as directed.
3. Share any concerns in relation to the treatment with the Specialist or GP.
4. Report any adverse effects to the Specialist or GP whilst taking the medication.
5. Attend booked appointments for review and monitoring whilst receiving growth hormone.

**Growth Hormone (Somatropin)**

Administration of recombinant human Growth Hormone (r-hGH) is by subcutaneous injection or needle free transjection, on a nightly single injection basis, in order to mimic the normal physiology of GH secretion. Depending on the brand chosen, the injections may be prepared from multi-dose ampoules or by using cartridges in a multi-dose pen injection device.

GH has a role in protein, lipid and carbohydrate metabolism, as well as in increasing linear growth in children.
EoE agreed indications for GH Therapy in Children

Growth hormone deficiency causing short stature
   Idiopathic isolated GH deficiency
   Congenital hypopituitarism e.g. anomalies of the pituitary gland such as seupto-optic
   dysplasia
   Acquired hypopituitarism e.g. craniopharyngioma & post cranial irradiation or neuro-
   surgery or traumatic brain injury

Turner Syndrome (Confirmed by chromosome analysis)
   Severe constitutional short stature amenable to GH therapy.

Chronic renal failure
   For the treatment of growth failure associated with this condition. Post renal transplant
   is a discontinuation criterion in the product SPCs.

SHOX deficiency

Prader-Willi syndrome.
   NB we do not currently advocate treatment of obese patients with Prader Willi syndrome,
   due to concerns over fatalities, without careful evaluation by sleep studies and ENT.

Small for Gestational Age (SGA)
   All the following criteria must be met:
   - Over 4 years of age and birth weight on or below 0.4th centile
   - More than 2SD below the average height for age (below the 3rd centile after the
     age of 5)
   - More than 2.5SD below the parental adjusted height standard deviation score
     (child's centile is more than 2.5 centiles less than the mean parental height
     centile)
   - Height velocity standard deviation score is less than 0 over the past year (child
     falling below their centile over the last year)

There are other disorders in which GH therapy may be indicated as an off label usage, including
Noonan syndrome, and skeletal dysplasias, IGF 1 Deficiency for example due to neurosecretory
dysfunction and CHARGE syndrome with short stature and IGF1 deficiency. These indications ALL
require approval via the individual funding route.

Diagnostic Criteria for GH Deficiency in Children

The early recognition of growth failure is an essential component of a national strategy leading to
rational and effective use of GH. Monitoring of growth (height and weight) should be part of all health
surveillance of children in primary care and in school. The diagnosis is based on a combination of the
following:

1. Short stature that is inappropriate for the parental heights: Height velocity > than 2.5 SD less
   than mid parental height centile (the patient's centile is > 2.5 SD less than the mid parental
   height centile)

2. Subnormal growth rate: ie height velocity below 25th centile, < 4cm/yr over 2 successive
   years, < 3rd centile over 1 year in pre-pubertal children, < 8cm/yr in puberty.

3. Other pituitary hormone deficiencies.

4. Growth delay confirmed by delayed skeletal maturation. Clinical and/or imaging evidence of a
   structural disorder of the hypothalamo-pituitary axis; this includes previous cranial irradiation.

5. Exclusion of other genetic, psychosocial and systemic causes of growth failure.
6. Biochemical evidence of GH deficiency defined as < 7 ug/L (or< 20 mU/L) peak to provocation test

7. IGF1 test result at lower end of normative range for sex and age (normative range to be stated); exception is where there is clear evidence of CNS pathology or prior radiotherapy, when growth stimulation test result showing deficiency is acceptable without a 2nd test result.

Growth Hormone Dosage in Children

**GH deficiency:**
0.7 – 1.0 mg/m²/day or 0.025 – 0.035 mg/kg/day given as a daily subcutaneous dose. *(upper end of dosing scale for pubertal child).*

**Prader-Willi syndrome and SGA:**
1.0 mg/m²/day or 0.035 mg/m²/day given as a daily subcutaneous dose.

**Chronic renal failure, Turner’s Syndrome and SHOX Deficiency:**
1.4 mg/m²/day or 0.05 mg/kg/day given as a daily subcutaneous dose.

**Adverse Effects**
In general side effects of r-hGH therapy are uncommon. Transient skin reactions and loss or increase of adipose tissue at injection sites can occur, particularly if the injection site is not rotated. In adult practice, r-hGH can lead to fluid retention and peripheral oedema but in children this is less of a problem. Therefore growth hormone should be stopped if the patient is undergoing major surgery. Fluid retention may play a role in the generation of raised intra-cranial pressure (benign intra-cranial hypertension). This may occur at the onset of GH therapy and is associated with severe headache and papilloedema. In such circumstances the therapy is discontinued for 2 – 3 weeks and then recommenced at a lower dose and gradually built back up to the full dose.

Growth hormone is associated with insulin insensitivity and there is a rise in serum insulin concentrations although blood glucose and glycosylated haemoglobin concentrations usually remain within normal limits. Consequently, patients with diabetes mellitus taking r-hGH may need their diabetic therapy adjusted. Consideration also needs to be given to the possible unmasking of diabetes in patient groups with a family history of Type 2 diabetes mellitus, and unmasking of potential ACTH deficiency.

The safety record is excellent. Antibody formation can be detected but is rarely of physiological relevance.

**Neoplasia:** Extensive surveys have **not** suggested an increased tumour or leukaemia risk with GH therapy, compared with similar patients who have not received GH therapy when replacement doses are physiological in confirmed GHD. Supra-physiological doses have not been used in this situation. What may be of more concern is the recent report from the UK that young adults treated with human pituitary GH up until 1985 had a higher mortality risk for colon cancer and non Hodgkin lymphomas than the general population (Swerdlow AJ, Higgins CD, Adlard P, Preece MA. Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959-85: a cohort study. Lancet 2002; 360: 273-7). It is however important to note that these data were collected on patients on high doses of human pituitary derived GH which may have also contained other growth factors. Although these data raise concern they do not provide firm evidence of an association. Long-term surveillance of patients receiving GH therapy irrespective of diagnosis is continuing through National Cancer Registries.

**Prader Willi Syndrome:** Prader-Willi Syndrome (PWS) is a rare genetic disorder with an incidence of approximately one in 10,000 births. In the first year of life it is characterised by hypotonia and failure to thrive, but in later years if energy intake is not restricted, severe obesity results. Other components of this syndrome include short stature which is now generally accepted to be associated with GHD.
As obesity is associated with reduced GH responses on testing, it was argued that the GH abnormality in PWS was not the primary problem. More detailed neuroendocrine studies, however, revealed that the majority of individuals with PWS have GHD. Randomised controlled studies of r-hGH in PWS have demonstrated an increase in short term linear growth analogous to that seen in patients with GHD. The r-hGH dosing schedule is similar to that used in GHD. Further data on final heights are now becoming available and are similar to those observed in GHD patients.

Although the value of increasing the stature of these individuals can be questioned, the effects of r-hGH treatment on body composition is perhaps of greater importance. Growth Hormone therapy leads to fat sparing and an increase in lean body mass. The latter is less obvious in PWS and is in contrast to the reports of increased muscle strength and agility. The observation of improved respiratory muscle function is of particular importance in these individuals.

To date the safety profile of growth hormone in PWS is similar to that observed in the GHD child. However, in severely obese PWS patients there appears to be a potential risk of sudden death associated with GH use (April 4, 2003. Addendum to the Pharmacia statement on recently reported cases of death in growth hormone treated patients with PWS, January 7, 2003). For this reason, we do not currently give GH to severely obese patients with PWS.

**Cost**

<table>
<thead>
<tr>
<th>Preparations of Somatropin Available in the U.K</th>
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<tbody>
<tr>
<td>These prices are applicable from June 2010</td>
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</tbody>
</table>

**COMMISSIONERS NOTE** that providers do not pay for growth hormone for 1st 3 months.

**COMMISSIONER REQUEST:** ONLY 3 COMPANY PRODUCT CHOICES TO BE DISCUSSED WITH CHILD AND CARER. THESE TO BE CHOSEN BY TAKING INTO CONSIDERATION THE CHEAPEST PRODUCT IN PRIMARY CARE.

<table>
<thead>
<tr>
<th>Growth Hormone</th>
<th>Dosage (milligrams)</th>
<th>Cost £/mg of growth hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotropin (Pfizer)</td>
<td>5.3 mg Pen cartridge</td>
<td>£23.18</td>
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<tr>
<td></td>
<td>12.0 mg Pen cartridge</td>
<td>£23.18</td>
</tr>
<tr>
<td></td>
<td>0.2-2.0mg MiniQuick, in 0.2mg increments</td>
<td>£23.18</td>
</tr>
<tr>
<td>Humatrope (Eli Lilly)</td>
<td>6 mg Pen cartridge</td>
<td>£18.00</td>
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<tr>
<td></td>
<td>12 mg Pen cartridge</td>
<td>£18.00</td>
</tr>
<tr>
<td></td>
<td>24 mg Pen cartridge</td>
<td>£18.00</td>
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<tr>
<td>Norditropin SimpleXx (Novo Nordisk)</td>
<td>5 mg Pen cartridge</td>
<td>£21.39</td>
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<tr>
<td></td>
<td>10 mg Pen cartridge</td>
<td>£21.39</td>
</tr>
<tr>
<td></td>
<td>15 mg Pen cartridge</td>
<td>£21.39</td>
</tr>
<tr>
<td>Nutropin Aq (Ipsen)</td>
<td>10 mg Pen cartridge</td>
<td>£20.70</td>
</tr>
<tr>
<td>Omnitrope (Sandoz)</td>
<td>5 mg Pen cartridge</td>
<td>£18.26</td>
</tr>
<tr>
<td>Saizen (Serono)</td>
<td>8.0 mg Click-Easy cartridge</td>
<td>£22.18</td>
</tr>
<tr>
<td>Zomacton (Ferring)</td>
<td>4 mg vial</td>
<td>£19.92</td>
</tr>
</tbody>
</table>

**Contact Numbers**

<table>
<thead>
<tr>
<th>Great Ormond Street Hospital</th>
<th>Telephone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switchboard</td>
<td>0207 405 9200</td>
</tr>
</tbody>
</table>
| Consultant                   | Professor Dattani  
Via switchboard |
| Registrar                    | Endocrine Registrar  
Bleep: 0281 |

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### Availability of Support and Advice

**Consultants**

Dr Caroline Brain  
Great Ormond Street Hospital Secretary: 020 7405 9200 extension 5813  
University College London Hospital Secretary: 020 7380 9445

Professor Gary Butler  
Great Ormond Street Hospital Secretary: 020 7405 9200 extension 5813  
University College London Hospital Secretary: 020 7380 9221

Professor Mehul Dattani  
Great Ormond Street Hospital Secretary: 020 7405 9200 extension 1017  
University College London Hospital Secretary: 020 7380 9445

Professor Peter Hindmarsh  
Great Ormond Street Hospital Secretary: 020 7405 9200 extension 5813  
University College London Hospital Secretary: 020 7380 9221

Dr Khalid Hussain  
Great Ormond Street Hospital Secretary: 020 7405 9200 extension 8331

Dr Catherine Peters  
Great Ormond Street Hospital Secretary: 020 7405 9200 extension 1017

Dr Helen Spoudeas  
Great Ormond Street Hospital Secretary: 020 7405 9200 extension 1017  
University College London Hospital Secretary: 020 7380 9455

**Endocrine Nurse Specialists**

Great Ormond Street - 020 7813 8214  
University College London Hospitals – 0845 1555 000 Ex 9204

**Endocrine Registrars**

Great Ormond Street Hospital 020 7405 9200 – Endocrine Registrar  
University College Hospital 0845 1555 000 – Paediatric Endocrine Registrar

**Patient Support Groups**

The Child Growth Foundation: 2 Mayfield Avenue, Chiswick, London W4 1PW Tel: 020 8994 7625

The Pituitary Foundation: (PitPat) of the Society for Endocrinology, 17/18 The Courtyard, Woodlands, Almondsbury, Bristol, BS12 4NQ Tel: 0117 927 3355

**Medical Information**

BSPED - www.bsped.org.uk  
NICE - www.nice.org.uk  
ESPE – www.eurospe.org

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