HUMAN GROWTH HORMONE (SOMATROPIN) FOR TREATMENT OF ADULT GROWTH HORMONE DEFICIENCY PRESCRIBING SUPPORT INFORMATION

SECTION 1: SITUATION AND BACKGROUND

What is Growth Hormone?
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.

NICE Guidance: NICE TA64, Human growth hormone (somatropin) in adults with growth hormone deficiency
Recombinant human growth hormone (somatropin) treatment is recommended for the treatment of adults with growth hormone (GH) deficiency only if they fulfil all three of the following criteria.

- They have severe GH deficiency, defined as a peak GH response of less than 9 mU/litre (3 ng/ml) during an insulin tolerance test or a cross-validated GH threshold in an equivalent test.
- They have a perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in the disease-specific 'Quality of life assessment of growth hormone deficiency in adults' (QoL-AGHDA) questionnaire.
- They are already receiving treatment for any other pituitary hormone deficiencies as required.

Indications for Treatment: adult growth hormone deficiency
Adult GH deficiency may be of adult onset or childhood onset and may occur as isolated GH deficiency or as part of multiple pituitary hormone deficiency. In adult onset, GH deficiency is commonly due to pituitary tumours or their treatment, and to cranial irradiation. Childhood-onset GH deficiency is often idiopathic and may continue into adulthood. Also, iatrogenic GH deficiency may occur in childhood or adulthood in survivors of childhood malignancy, as a result of previous cranial irradiation and/or chemotherapy. The Society for Endocrinology estimates that approximately 1750 adults with GH deficiency currently receive treatment in the UK.

When will GPs be asked to prescribe?
Patients are given a three month dose titration period, during which time the dose of GH will be adjusted to achieve serum IGF-1 in the upper half of the normal range. This is followed by a six month therapeutic trial period; QoL-AGHDA score should be recorded at the end of the therapeutic trial period. GH is supplied by homecare companies. During this initial nine month trial period, the hospital clinic prescribes GH when requested by the homecare company.

Patients who have completed the therapeutic trial period and demonstrated an objective response in symptoms and QoL should be offered the opportunity to continue with treatment. If the patient meets these criteria, the patient’s GP will be asked to take on prescribing of GH after 9 months. However, the hospital specialists will continue to undertake monitoring of relevant parameters. GPs will prescribe on an FP10 prescription when requested by the homecare company.
## SECTION 2: BRANDS AND INJECTION DEVICES

### Preparations available

The hospital clinic will recommend which particular preparation should be started; several factors influence the choice of GH replacement therapy, including the dose and frequency of injections.

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<thead>
<tr>
<th>Preparation</th>
<th>Description</th>
<th>Available Doses</th>
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<tbody>
<tr>
<td>Genotropin</td>
<td>Go Quick pre-filled pen:</td>
<td>- 5.3mg (50mcg increments)  - 12mg (75mcg increments)</td>
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<tr>
<td></td>
<td>Two-chamber cartridge for reconstitution to be used in a pen device:</td>
<td>- 5.3mg (50mcg increments)  - 12mg (75mcg increments)</td>
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<td></td>
<td>MiniQuick single use two-chamber pen for reconstitution:</td>
<td>- 0.2mg up to 2mg (in 200mcg increments)</td>
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<tr>
<td>Norditropin</td>
<td>Nordiflex pre-filled pen:</td>
<td>- 5mg (25mcg increments)  - 10mg (50mcg increments)  - 15mg (75mcg increments)</td>
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<td></td>
<td>SimpleXx cartridge to be administered using NordiPen device:</td>
<td>- 5mg (50mcg increments)  - 10mg (50mcg increments)  - 15mg (100mcg increments)</td>
</tr>
<tr>
<td>Humatrope</td>
<td>Cartridges for administration by HumatroPen device:</td>
<td>- 6mg (25mcg increments)  - 12mg (50mcg increments)  - 24mg (100mcg increments)</td>
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<tr>
<td>Nutropin Aq</td>
<td>Formulary approved but not routinely prescribed by CUH.</td>
<td>10mg cartridge to be administered using NutropinAq Pen (100mcg increments)</td>
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<tr>
<td>Omnitrope</td>
<td>Formulary approved but not routinely prescribed by CUH.</td>
<td>Cartridge to be administered using SurePal device:  - 5mg (50mcg increments)  - 10mg (100mcg increments)  - 15mg (100mcg increments)</td>
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<td></td>
<td>Cartridge to be administered using Omnitrope Pen 5 or Pen 10 device:</td>
<td>- 5mg (50mcg increments)  - 10mg (100mcg increments)</td>
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<tr>
<td>Saizen</td>
<td>Non-formulary.</td>
<td>Cartridge to be administered by EasyPod autoinjector:  - 5.83mg  - 8mg</td>
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<td></td>
<td></td>
<td>Click.Easy 8mg cartridge to be administered by EasyPod autoinjector or One.Click autoinjector.</td>
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<tr>
<td>Zomacton</td>
<td>Formulary approved but not routinely prescribed by CUH.</td>
<td>- 4mg vial to be reconstituted and administered by syringe, ZomaJet 2 Vision or Ferring-Pen</td>
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<td></td>
<td>- 10mg vial to be reconstituted and administered by syringe or Zomajet Vision X needle-free device</td>
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Additional injection device considerations
Once the hospital clinic has recommended the most appropriate growth hormone delivery system, the homecare company associated with GH brand provide the training kit and teach the patient how to use the device. Injection pens/needles/syringes/swabs and disposal boxes for sharps are provided by the homecare company.

SECTION 3: PRESCRIBING INFORMATION

Dosage and administration
Treatment is self-administered by a daily subcutaneous injection.

- The initial dose is 0.2-0.3mg daily.
- For the first three months dosage adjustments are made after assessments of serum levels of IGF-1, and in response to the presence of adverse effects, until a maintenance dose is achieved.
- The median maintenance dose is 0.4 mg daily.
- GH requirements may decrease with age.

Contraindications:

- Any evidence of tumour activity:
  - Prior anti-tumour therapy must be completed before starting GH therapy.
  - Treatment should be discontinued if there is evidence of tumour growth.
- Critically ill patients (heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions).
- Renal transplantation (discontinue at transplantation).
- Patients with known hypersensitivity to GH or to any of the excipients.
- Pregnancy or lactation.

Cautions:

- Diabetes mellitus (adjusting of antidiabetic therapy may be necessary)
- History of malignant disease (see below)
- Hypoadrenalism (initiation or adjustment of glucocorticoid replacement therapy may be necessary)
- Hypothyroidism
- Papilloedema (see below)
- Resolved intracranial hypertension (monitor closely)

Adverse effects

- Growth hormone deficient patients are characterised by extracellular volume deficit. When treatment with somatropin is initiated, this deficit is corrected. Fluid retention with peripheral oedema may occur.
- In case of severe or recurrent headache, visual problems, nausea and/or vomiting, a funduscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and, if appropriate, the growth hormone treatment should be discontinued.
- Carpal tunnel syndrome is uncommon but may be seen in adults. The symptoms are usually transient, dose dependent and may require transient dose reduction.
- Other mild side effects include headache, myalgia, mild hypertension, visual problems, and nausea/vomiting.
- Antibody formation can be detected but is rarely, if ever, of physiological relevance.
• Local injection site reactions are unusual and are generally due to unnecessary use of a spirit-based skin cleanser.
• GH is potentially diabetogenic (insulin resistance and hyperglycaemia) but international studies have shown that the incidence of permanent diabetes is not increased with treatment.
• There is no possibility of contamination with a slow virus as occurred with preparations of pituitary-derived growth hormone.

Is there a risk of malignancy?
There is no evidence for increased risk of new primary cancers in children or in adults treated with somatropin. In patients in complete remission from tumours or malignant disease, somatropin therapy has not been associated with an increased relapse rate.

An overall slight increase in second neoplasms has been observed in childhood cancer survivors treated with growth hormone, with the most frequent being intracranial tumours. The dominant risk factor for second neoplasms seems to be prior exposure to radiation. Patients who have achieved complete remission of malignant disease should be followed closely for relapse after commencement of somatropin therapy.

Drug Interactions
• Growth promoting effect may be inhibited when combined with corticosteroids (including inhaled or topical).
• Increased doses of GH may be required if on oestrogen replacement therapy. Conversely the dose of GH may need to be reduced if oestrogen is stopped.
• Anti-diabetic therapy (including insulin) may require adjustment owing to potential insulin resistance and hyperglycaemia.
• The manufacturers note a theoretical risk of induction of CYP450 isoforms (including 3A4); the clinical significance is unknown.

Monitoring
IGF-1 is tested according to the following schedule:
• Baseline
• Month 1, month 3: dose titration period. The dose of GH will be adjusted during this time to achieve serum IGF-1 in the upper half of the normal range.
• Month 6, month 9: therapeutic trial period. QoL-AGHDA score should be recorded at the end of the therapeutic trial period (see below).
• If GH continues following the therapeutic trial period, the patient will be assessed in the hospital clinic at least annually. GH requirements may decrease with age.

GPs will not be expected to undertake near patient testing to monitor this therapy. Where appropriate, results of the specialists’ biochemical surveillance will be made known to each patient’s GP practice.

If IGF-1 levels are found to be higher than patient’s normal range, the dose of GH is reduced and IGF-1 level repeated after one month.

Treatment cessation criteria
The QoL status of people who are given GH treatment should be re-assessed 9 months after the initiation of therapy (an initial 3-month period of GH dose titration, followed by a 6-month therapeutic trial period). GH treatment should be discontinued for those people who demonstrate a QoL improvement of less than 7 points in QoL-AGHDA score.
References
NICE technology appraisal guidance [TA64]. Published date: August 2003; reviewed date: November 2014. Human growth hormone (somatropin) in adults with growth hormone deficiency. https://www.nice.org.uk/guidance/ta64

Summary of product characteristics for each drug are available at the Electronic Medicines Compendium: https://www.medicines.org.uk/emc

BNF online: https://bnf.nice.org.uk/

Document Management

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<th>Document ratification and history</th>
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