Synthetic Recombinant Human Growth Hormone (Somatropin)

This shared care guideline provides the necessary information and guidance for the shared care of adult patients requiring synthetic recombinant human Growth Hormone (Somatropin) therapy

Introduction
Synthetic recombinant growth hormone (somatropin) is a bio-engineered peptide with sequence identical to human pituitary growth hormone that is administered as a single daily subcutaneous injection in the evening.

National Guidance (NICE TAG 64) guidance on the use of growth hormone (GH) in adults with growth hormone deficiency

- NICE has recommended that recombinant human growth hormone should be used **ONLY in adults with severe growth hormone deficiency that is severely affecting their quality of life.**

- Recombinant human growth hormone is only recommended for the treatment of adults with growth hormone deficiency **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 (ITT) 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.

- 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

- Patients **who develop GH deficiency in early adulthood, after linear growth is completed but before the age of 25 years**, should be given GH treatment **until adult peak bone mass has been achieved, provided they satisfy the biochemical criteria for 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). After adult peak bone mass has been achieved, the decision to continue GH treatment should be based on all the criteria in the 2nd bullet point above.

- Patients currently receiving GH treatment, for the management of adult onset GH deficiency, whether as routine therapy or as part of a clinical trial, could suffer loss of well being if their treatment were to be discontinued at a time they did not anticipate. Because of this, all NHS patients who are on therapy at the date of publication of this guidance should have the option to continue treatment until they and their consultant consider it is appropriate to stop.
Initiation of GH treatment, dose titration and assessment of response during trial periods should be undertaken by a consultant endocrinologist with a special interest in the management of GH disorders. Thereafter, if maintenance treatment is to be prescribed in primary care, it is recommended that this should be under an agreed shared-care protocol.

**Clinical Need**

- Growth hormone is produced by the anterior pituitary gland. It has a role in the regulation of protein, lipid and carbohydrate metabolism, as well as in increasing growth in children. Its secretion is intermittent and occurs predominantly during deep sleep. Secretion reaches maximal levels during adolescence, and then declines with age by approximately 14% per decade.

- 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 the prevalence of adult-onset GH deficiency is approximately 1 in 10,000 of the adult UK population. If adults with childhood-onset GH deficiency are also considered, the prevalence may be as high as 3 in 10,000 of the adult population. This equates to between approximately 60 and 180 adults with GH deficiency in Oxfordshire.

- GH deficiency in adults may be associated with the following adverse features to a variable degree in any individual: reduced quality of life (QoL) especially reduced energy levels; altered body composition (reduced lean mass and increased fat mass, especially in the trunk); osteopenia/osteoporosis (reduced bone mineral density); dry skin (reduced sweating); reduced muscle strength and exercise capacity; lipid abnormalities (especially elevated LDL cholesterol); insulin resistance; increased levels of fibrinogen and plasminogen activator inhibitor; reduced extracellular fluid volume; increased thickness of the intima media of blood vessels; and impaired cardiac function.

**Patients under Clinical Suspicion**

- Patients with known or suspected hypothalamic or pituitary disease
- Patients who have received cranial irradiation
- Patients with a deficiency or one or more of the other pituitary hormones
- Patients who have undergone hypophysectomy
- Adults who received growth hormone in childhood for GHD
Diagnosis of Growth Hormone Deficiency

- Patients with severe GH deficiency in adulthood are defined as patients with known hypothalamic pituitary abnormality and at least one known deficiency of another pituitary hormone excluding prolactin.

- These patients should undergo a single diagnostic test in order to diagnose the presence of GH deficiency.

- In patients with childhood onset isolated GH deficiency (no evidence of hypothalamic pituitary abnormality or cranial irradiation), two diagnostic tests should be recommended, except for those having low IGF-1 (a marker of GH response) concentrations (standard deviation score less than -2) who may be considered for one test.

- Several tests are available for the diagnosis of GH deficiency. The ITT is regarded as the ‘gold standard’ test for adults.

- A general definition of severe GH deficiency in adults is a peak concentration of less than 9 mU/litre (3 ng / ml) in response to insulin-induced hypoglycaemia.

- When the ITT is contraindicated other tests – such as response to GH-releasing hormone, arginine or glucagon – can be used.

When to Test

- Diagnostic test after stabilised treatment of other pituitary deficiencies
- Diagnostic test at least one month after pituitary surgery
- Childhood treatment should be interrupted for a period of 2-3 months before retesting of growth hormone level status.

Dose and administration

- Treatment is self-administered by a daily subcutaneous injection. The initial dose is 0.2–0.3 mg (0.6–0.9 IU) daily (typically 0.27 mg [0.8 IU] daily).

- For the first 2–3 months dosage adjustments are made after monthly assessments of serum levels of IGF-1, and in response to the presence of adverse effects, until a maintenance dose is achieved. The currently used median maintenance dose is 0.4 mg (1.2 IU) daily.

- GH requirements may decrease with age, mirroring the physiological production of growth hormone and may vary with weight and possibly gender.

Assessment at 3 months

- The decision to continue therapy should be taken after a further discussion between the patient, the GP and the endocrinologist.

- The decision will be based on a number of factors. The improvement noted in quality of life and any return to a more normal body composition should be taken into account. In addition, the long term effects of cardiovascular risk factors will be considered since epidemiological evidence suggests that GH-deficiency in adults increases the risk of cardiovascular disease\(^1\).
Continuing Therapy

- The optimal management of patients continuing with their GH replacement therapy after the assessment period will depend on the shared care co-operation between hospital and general practice.

- The consultant should carry out a further review of benefit after 9 months (an initial 3 month period of GH dose titration, prescribed by the consultant followed by a 6 month therapeutic trial period, prescribed by the patients GP) after the initiation of therapy by measuring the patient’s QoL status.

- The consultant should ensure that GH treatment is only continued for those people who demonstrate a QoL improvement of more than 7 points in QoL-AGHDA score.

Preparations available

- GH is licensed for replacement therapy in adults with severe growth hormone deficiency.

- The use of the Omnitrope (Sandoz) or Genotropin (Pharmacia) range as the preferred 1st choice product for new patients who are eligible for treatment with growth hormone (in accordance with NICE guidance) is currently recommended, in line with NHS South Central Guidance to Support Cost-effective Choice of Growth Hormone (Somatropin) Products.

- Saizen (Merck Serono) is reserved for patients whose compliance is poor as it includes a computerised chip in the device which allows the prescriber to assess the number of doses taken and missed.

- Zomacton (Ferring) is reserved for needle phobic patients.

- Where appropriate, consideration will be given to switching patients on other growth hormones.

- Each product is produced by recombinant DNA technology and has a sequence identical to that of human GH.

- Growth hormone is given by subcutaneous injection which the patient would be expected to self-administer. Physiological growth hormone release peaks during sleep therefore the injection is given in the evening before bedtime.

- Training facilities for the patients to self-inject will be established within secondary care.

- The hospital will also be responsible for provision of injection devices or appropriate injection aids and materials, for the entire duration of therapy even under general practitioner management.

Adverse effects

- Fluid retention (peripheral oedema) is the most commonly reported “side effect” of GH replacement therapy. Fluid retention, with occasional mild ankle oedema, is a normal part of growth hormone action. This tends to decrease as therapy continues but may occasionally require dose reduction.

- Hyperglycaemia and hypoglycaemia have been reported. GH therapy has also been shown to reduce insulin sensitivity in these patients by antagonising the action of insulin – this could increase the risk of diabetes.

- Headache:- persistent headaches require investigation with fundoscopy for papilloedema being recommended if severe or recurrent headache, visual problems or nausea and vomiting occur and if papilloedema is confirmed consider benign intracranial hypertension (rare cases reported). This is usually recognised shortly after commencement of therapy. Usually a temporary cessation of treatment resolves the symptoms. A severe and persistent headache should be reported immediately to the endocrinology department.

- Arthralgia (joint pain), myalgia (muscle pain), carpal tunnel syndrome and paraesthesia can occur. These effects, if they occur, are usually mild and self-limiting. A reduction in the GH dose may be required while they persist.
Hypothyroidism can occur

Reactions at injection site – these are unusual and may also be due to unnecessary use of a spirit-based skin cleanser.

Antibody formation can be detected but is rarely of physiological relevance.

Other side effects may include mild hypertension, visual problems and nausea and vomiting.

All of these possible side-effects will have been discussed with the patient by the endocrine team before treatment is started and an information leaflet provided.

There is no evidence to suggest that GH therapy will increase the risk of abnormal or neoplastic growth, either a new growth or a resurgence of an old tumour.

Contra-indications

GH treatment is contraindicated in people with any evidence of tumour activity, with proliferative diabetic retinopathy, in critically ill patients (for example, after complications following open heart or abdominal surgery, multiple trauma, acute respiratory failure or similar conditions) and also in patients with known hypersensitivity to GH or to any of the excipients.

In patients with tumours, anti-tumour therapy must be completed before starting GH therapy.

Pregnancy and lactation

GH treatment is contraindicated during pregnancy and lactation.

Drug interactions (refer also to BNF or SPC)

Corticosteroids: The growth promoting effect of somatropin may be inhibited by corticosteroids

Oestrogens: Increased doses of somatropin may be needed when given with oestrogens (when used as oral replacement therapy)

Monitoring

A recognised technique for monitoring the dose is to take regular measurements of insulin-like growth factor I (IGF-I). IGF-I levels should increase during therapy. IGF-I levels should normally be maintained within the normal range during therapy. The aim is to find the dose of GH which moves IGF-I levels into the normal range.

(* In discussion with GP and patient it may be appropriate to carry out a therapeutic assessment of 3 – 6 months).

The patient will require one or two monthly IGF-I blood tests until the optimum maintenance dose is reached.

Under shared care guidelines these tests may be taken at the GP surgery as appropriate and the result discussed between the hospital endocrinologist and GP. (If testing facilities are unavailable arrangements should be made with the hospital). The dose of growth hormone should be adjusted as necessary.

Patient information leaflet

Patients should be supplied with an information leaflet from the manufacturer.
Shared Care Responsibilities
Shared care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients should be under regular follow-up which provides an opportunity to discuss drug therapy.

a) Hospital Consultant

On diagnosis each patient should have a full clinical assessment and series of tests to produce a comprehensive baseline from which any subsequent change can be monitored.

Clinical Assessment INITIALLY
- Current medical history
- Full history of hypothalamic-pituitary disease
- Surgical and radiological history
- Number of pituitary hormone deficiencies
- Current replacement regimen
- Previous growth hormone treatment (if any)
- Quality of life assessment using the disease-specific ‘Quality of life assessment of growth hormone deficiency in adults’ (QoL-AGHDA) questionnaire.

Medical and Biochemical Assessment ANNUALLY
- Height, weight and body mass index
- Blood pressure
- HbA1c
  - Lipid profile
- Serum IGF-I (insulin-like growth factor-I)
- Body composition measurement
- Waist/hip ratio
- Recent pituitary imaging (MRI or CT scan) as appropriate
- Visual field measurement, where relevant
- Assessment of quality of life

PLUS
- Monitoring patients overall health and well-being
- Liaison with the GP on patient’s progress
- Adjustment of the dose where appropriate
- Discussion with the patient of any adverse effects
- Training, monitoring of self-administration and compliance

- The initial assessment period of 3 months will allow for prescribing, adjustment and stabilisation of the dose of growth hormone by the consultant.

- Ensure the patient understands the nature and complications of drug therapy and their role in reporting adverse effects promptly and is trained on the appropriate injection device.

- Write to the GP requesting shared care and outline shared care protocol criteria.

- The consultant should carry out a review of benefit 9 months (an initial 3 month period of GH dose titration, prescribed by the consultant followed by a 6 month therapeutic trial period, prescribed by the patient’s GP) after the initiation of therapy by measuring the patient’s QoL status.

- The consultant should ensure that GH treatment is discontinued for those people who demonstrate a QoL improvement of less than 7 points in QoL-AGHDA score.
• Liaise with GP regarding changes in disease management, drug dose, and missed clinic appointments.

• Ensure clinical supervision of the patient is done by follow-up as appropriate.

• Be available to give advice to GP and patient.

b) GP

• Prescribe synthetic growth hormone (somatropin) after 3 months of dose stabilisation, review of benefit and prescribing by the consultant.

• Advise the hospital consultant of any clinical changes where appropriate.

• Monitor for adverse effects as detailed above.

• Carry out an annual or bi-annual (as appropriate) medical check to occur six months after each annual hospital visit comprising:
  - Height, weight and body mass index
  - Blood pressure
  - HbA1C
  - Lipid profile
  - IGF-I (if appropriate for GPs locally)

PLUS

• Monitoring overall patient health and well being
• Observation and report of any unexpected side-effects to the hospital endocrinologist (severe headaches to be reported immediately)
• Monitoring of self administration and compliance in consultation with specialist nurse (checking that prescribed dose is being used)
• Liaison with hospital endocrinologist to reach joint decision about further treatment.

c) Patient

• Report any adverse effects to their GP and/or consultant.

• Attend all out-patients and GP appointments for regular monitoring as outlined above.

Availability of support and advice

• Consultant: Professor Ashley Grossman and Dr Niki Karavitaki

• Specialist Nurse: Anne Marland