Synthetic Recombinant Human Growth Hormone (Somatropin) (TLS Amber)

for the use in children with growth failure as defined by NICE TA188[1]

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines how responsibility for prescribing **somatropin for children with growth failure** might be shared between specialist and general practitioner (GP). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients and parents are consulted about treatment and are in agreement with it.

The doctor who prescribes this medication legally assumes clinical responsibility for **somatropin** and the consequences of its use.

RESPONSIBILITIES and ROLES

A child with confirmed Growth Hormone (GH) deficiency who is otherwise stable does not require frequent hospital supervision, with generally 6 monthly out-patient visits, so he or she will remain the primary responsibility of their GP. Patients should be under regular follow-up which provides an opportunity to discuss drug therapy.

Hospital Consultant's responsibilities

1. To confirm the child meets the diagnostic criteria for GH therapy (see below).
2. To confirm the child has no contraindications to GH therapy and consider the relevance of any cautions.
3. To ensure the compatibility of GH with concomitant medicines at the time of initiation (and at subsequent reviews).
4. To ensure the child and their family understands the nature, benefits and complications of GH therapy and their role in reporting adverse effects promptly.
5. To determine the dose and frequency of GH injections and, in conjunction with the child and their family, decide upon the most appropriate injection device. It is important to note here that the brand of somatropin and type of injection device will be considered in order of increasing cost, so as to ALWAYS ensure that the child is initiated on the most cost-effective brand and injection device that they or their family are able to use.
6. To initiate GH therapy and provide an FP10 prescription for the home delivery service for at least the first 28 days' supply of somatropin.
7. To arrange for the child and their family to be instructed in the storage, preparation and administration of GH injections
8. To write to the child's GP to outline the need for GH therapy and ask whether he or she is willing to participate in shared care; to provide a copy of this shared care protocol for information and not to transfer prescribing responsibility until the GP has formally agreed to share care in this way.
9. To discuss the possibility of shared care with the child and their family and obtain their consent.
10. To review the patient's growth and general condition *at least 6 monthly*, including height and weight measurements, bone age assessment and hormone measurement as indicated.
11. To review the child's GH dosage, guided by height velocity and pubertal stage.
12. To audit the patient's response to GH therapy compared to nationally agreed criteria.
13. To review associated drug therapy.
14. To promptly advise the child's GP as to continued justification for, or the need to stop, GH therapy.
15. To promptly communicate to the GP changes in disease management, drug dose, missed appointments, etc.
16. To be available, and to ensure clear back-up arrangements are in place when not available, to give advice and support to the GP, the child and their family.
17. To report adverse events to the Medicines & Healthcare Products Regulatory Agency (MHRA) and the child's GP.

General Practitioner's responsibilities

1. Prior to initial referral, to provide the child and their family with advice on the reason for referral and the potential role of investigation and therapy for the child's growth problem.
2. To reply to the request to share care from the child's hospital consultant as soon as practicable.
3. To ensure a full understanding of their responsibilities for managing a child with growth failure on GH, including identification of side-effects in line with the relevant Summary of Product Characteristics (SPC).
4. To prescribe GH at the dose and frequency, and in the injection device, recommended by the child's hospital consultant.
5. To ensure the compatibility of GH with newly-prescribed concomitant medication.
6. To report to, and seek advice from, the hospital consultant if any aspect of the child's care is of concern.
7. To advise the hospital consultant of any clinical changes where appropriate.
8. To monitor the child for adverse effects of GH therapy as detailed below and report any adverse effects which occur to the paediatric endocrine consultant and the MHRA.
9. To stop treatment on the advice of the child's hospital consultant.

Please note: there is no requirement for primary care blood testing.

Child, Parent or Guardian's role
1. To attend all appointments with the child's GP and hospital consultant. 2. To agree to regular monitoring as outlined above. 3. To share any concerns they have in relation to treatment with GH with the child's GP or hospital consultant. 4. To inform the child's GP and hospital consultant of all other medicines taken, including over-the-counter medicines. 5. To report any clinical changes to the child's GP and/or hospital consultant. 6. To promptly report any adverse effects to the child's GP and/or hospital consultant.

BACK-UP ADVICE AND SUPPORT

Contact details	*Telephone No.*	*Bleep No.*	*Email address*
Janet King Consultant Paediatrician (Growth Clinic)	01793- 604269	2120	janet.king@gwh.nhs.uk
Sanjay Rathi, Consultant Paediatrician	01793- 604925	1358	sanjay.rathi@gwh.nhs.uk
Cathy Dewdney, Lead Pharmacist (Paediatrics)	01793- 605193	1327	cathy.dewdney@gwh.nhs.uk
GWH Medicines Information	01793 - 605029	-	medicines.information@gwh.nhs.uk

SUPPORTING INFORMATION

Therapeutic summary
Somatropin is a bio-engineered peptide with a sequence identical to that of human pituitary growth hormone, which increases growth by a direct action on the growth plates and by production of insulin-like growth factors (especially IGF-1), mainly in the liver. It also has important effects on the metabolism of proteins, lipids and carbohydrates, not only during childhood, but also throughout adult life.

Licensed indications
In the UK, there are 7 licensed preparations of somatropin available: Genotropin (Pfizer); Humatrope (Lilly); Norditropin (Novo Nordisk); NutropinAq (Ipsen); Omnitrope (Sandoz); Saizen, (Merck Serono) and Zomacton (Ferring). Their licensed indications are as follows:

- growth disturbance in children due to insufficient secretion of growth hormone (growth hormone deficiency)
- growth failure in girls associated with gonadal dysgenesis (Turner syndrome)
- growth retardation in prepubertal children associated with chronic renal insufficiency (CRI)
- improvement of growth and body composition in children with Prader–Willi syndrome. The diagnosis of Prader–Willi syndrome should be confirmed by appropriate genetic testing.
- growth disturbance (current height standard deviation score [SDS] < −2.5 and parental adjusted height SDS < −1) in short children born small for gestational age, with a birth weight and/or length below −2 SD, who failed to show catch-up growth (height velocity SDS less than 0 during the past year) by 4 years of age or later.
- growth failure associated with *SHOX* deficiency, as confirmed by DNA analysis

Please refer to SPCs for more detailed information http://www.medicines.org.uk

Supporting evidence & expected / established place in treatment pathway
NICE guidance (NICE TA188) recommends the use of human growth hormone (somatropin) for the treatment of children with growth failure due to:

- proven Growth Hormone (GH) Deficiency, supported by appropriate auxological, biochemical and radiological investigations

- Turner's 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.

- Prader-Willi syndrome

- Chronic renal insufficiency (CRI) before puberty providing:
  - Nutritional status has been optimised
  - Metabolic abnormalities have been optimised
  - Steroid therapy has been reduced to minimum.

- Small for gestational age, with a length and weight at birth which was 2 standard deviations below the population average, and with subsequent growth failure at 4 years or age or later.

- proven Short Stature Homeobox-containing gene (*SHOX*) deficiency

It also advises that:

- 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. If, after that discussion, more than one product is suitable, the least costly product should be chosen.
- Treatment should not be discontinued by default. The decision to stop treatment should be made in consultation with the patient and/or carers either by:

    - a paediatrician with specialist expertise in managing growth hormone disorders in children, or
    - an adult endocrinologist, if care of the patient has been transferred from paediatric to adult services.

Referral Criteria
Children with inappropriate short stature and/or subnormal growth rates should be referred to a hospital specialist with expertise in their assessment.

Diagnostic criteria for GH deficiency
Monitoring of growth (height and weight) should be part of all health surveillance of children in primary care and in school and will allow early recognition of growth failure.

a) Short stature that is inappropriate for parental heights
b) Subnormal growth rate; a height velocity of below the 25th centile or less than 5cm per year in a prepubertal child.
c) Clinical and/or imaging evidence of a structural disorder of the hypothalamopituitary axis; this includes previous cranial radiation.
d) Exclusion of other genetic, environmental and systemic causes of growth failure.
e) Biochemical evidence of GH deficiency.

Duration of GH Therapy
This is determined by:

- Age at diagnosis of GH deficiency
- Age at which epiphyseal fusion and final adult height is achieved. 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.
- Response to GH treatment: treatment should normally be discontinued if there is a poor response (defined as an increase in growth velocity of less than 50% from baseline, in the first year of therapy.)
- At final height GH therapy will normally be discontinued but patients will require retesting of GH status. If they remain GH deficient, GH will be restarted but at a lower dose (initially 0.2–0.4 mg daily).

Additionally 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.

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.

Preparations available

- Injections may be given from multi-dose vials, cartridges via pen-injector / needle-free devices or disposable single-dose pens.

- 7 pharmaceutical companies currently market GH in the UK: Pharmacia, Novo Nordisk, Merck Serono, Ipsen, Lilly, Sandoz and Ferring. All preparations have similar growth promoting properties and excellent safety profiles.

- Costs per mg vary considerably. The most cost-effective product will always be considered first, but there are important differences in delivery devices and formulation which may determine the specific preparation chosen.

- The patient and their family will be involved in the choice of preparation.

Injection Equipment
The current arrangement is that GH manufacturers, through their customer care services, make available a range of injection devices. Storage containers, needles and safety bins are also provided by the manufacturers. The Children's Community Service arrange this.

Dosage and administration

- ***GH deficiency in pre-pubertal child:*** 5 mg/m^2/week divided into 7 daily doses.
- ***GH deficiency in pubertal child:*** 7 mg/m^2/week divided into 7 daily doses. Dosage is guided by height response and pubertal progress.
- ***Turner's syndrome and chronic renal failure:*** 10 mg/m^2/week divided into 7 daily doses. Dosage is guided by height response.
- ***Prader- Willi syndrome:*** 7 mg/m^2/week divided into 7 daily doses. Max 2.7 mg daily
- ***Small for gestational age:*** 7 mg/m^2/week divided into 7 daily doses.
- ***SHOX deficiency:*** 45-50mcg/kg per day.

Please refer to SPCs for more detailed information http://www.medicines.org.uk

Contra-indications and cautions

Somatropin is contraindicated in:

- Hypersensitivity to any of the active substance or any excipients
- Evidence of tumour activity (complete anti-tumour therapy and ensure intracranial lesions inactive before starting)
- Not to be used after renal transplantation or for growth promotion in children with closed epiphyses (or near closure in Prader-Willi syndrome)
- Severe obesity, severe respiratory impairment or sleep apnoea in Prader-Willi syndrome
- Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with Genotropin.

It should be used with caution in:

- Diabetes mellitus
- Papilloedema
- Relative deficiencies of other pituitary hormones
- History of malignant disease
- Disorders of the epiphysis of the hip
- Resolved intracranial hypertension
- Initiation close to puberty in a child born small for gestational age
- Silver-Russell syndrome

Please refer to SPCs for more detailed information http://www.medicines.org.uk

Side-effects

- Fluid retention and peripheral oedema can occur
- Arthralgia, myalgia, carpal tunnel syndrome and paraesthesia can occur
- Hypothyroidism can occur
- Reactions at injection site – these are unusual may be due to unnecessary use of a spirit-based skin cleanser.
- Transient local skin reactions
- Antibody formation can be detected but is rarely of physiological relevance.
- Diabetes mellitus; international figures demonstrate that incidence is not increased however insulin resistance, hyperglycaemia and hypoglycaemia have been reported
- Leukaemia in children with growth hormone deficiency has also been reported; a significant number of children selected to receive GH are at risk of primary tumour recurrence or a secondary tumour. Extensive surveys have not suggested increased risk with GH therapy.
- Persistent headaches require investigation. Fundoscopy is 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.
- Slipped femoral epiphysis is occasionally recognised shortly after commencement of therapy. Hip and knee pain or limp should therefore be investigated.
- All of these possible side-effects will have been discussed with the family by the endocrine team before treatment is started and an information leaflet provided.

Please refer to the SPCs for a full list of adverse effects & further information http://www.medicines.org.uk.

This medicine does not have black triangle (▼) status, but serious suspected reactions (even if well recognised or causal link uncertain) should be reported to the MHRA.

GP monitoring

- There is no requirement for blood testing to be undertaken in primary care.
- GPs are asked to monitor the child for, and advise the hospital consultant of, any clinical changes of concern.

- GPs are asked to monitor the child for adverse effects of GH therapy as detailed above and report any adverse effects which occur to the paediatric endocrine consultant and the MHRA.

Drug Interactions

- *Corticosteroids*
  - Somatropin has been reported to modestly reduce serum cortisol levels in GH deficient patients, so patients receiving corticosteroid replacement therapy may require an increase in their maintenance or stress doses of corticosteroid if given somatropin. This is especially true for patients on cortisone acetate or prednisone.
  - Glucocorticoid therapy may attenuate the growth- promoting effects of somatropin, so patients with GH and glucocorticoid deficiency may require careful adjustment of glucocorticoid dose to avoid both hypoadrenalism and an inhibitory effect on growth.
- *Antidiabetics*
  - Somatropin may cause hyperglycaemia and increased insulin resistance. When somatropin is initiated in an insulin-dependent diabetic, their blood glucose should be monitored more frequently and their insulin dose adjusted accordingly. One manufacturer advises similar caution with all antidiabetic therapy.
- *CYP3A4 substrates*
  - One study of somatropin in patients with GH deficiency reports that somatropin can induce cytochrome P450 isoenzymes, in particular CYP3A4, and that it may therefore increase the clearance and reduce plasma levels of drugs metabolised by CYP3A4, most especially sex hormones, antiepileptics and ciclosporin. There is little evidence to suggest that antiepileptics, other than carbamazepine, are metabolised to a clinically- relevant extent by CYP3A4 and there have been no reports interactions between somatropin and CYP3A4- metabolised drugs. However, it would seem prudent to monitor patients on oestrogens, testosterone, antiepileptics and ciclosporin more closely if initiating somatropin.

Please refer to SPCs for more detailed information http://www.medicines.org.uk

Storage

The storage requirements of un-opened or un-reconstituted preparations of somatropin vary depending on the brand prescribed and so manufacturers' instructions should ALWAYS be consulted. Once opened, reconstituted or otherwise in use, most manufacturers recommend storage at 2-8 ºC for a maximum of 28 days before discarding.

Please refer to SPCs for more detailed information http://www.medicines.org.uk

Cost

The costs of the different somatropin products (excluding VAT; 'British National Formulary' [BNF] edition 62) are: £23.18 per mg for Genotropin, £18.00 per mg for Humatrope, £21.27 per mg for Norditropin, £20.30 per mg for Nutropin, £17.53 per mg for Omnitrope, £23.18 per mg for Saizen and £19.92 per mg for Zomacton.

References

1. National Institute for Health and Clinical Excellence Technology Appraisal Guidance. NICE TA188: Human Growth Hormone for the treatment of growth failure in children. National Institute for Health and Clinical Excellence. May 2010.
2. British Medical Association and Royal Pharmaceutical Society. British National Formulary: BNF 62. BMJ Group and Pharmaceutical Press. September 2011.
3. Stockley's Drug Interactions. Accessed on 6th December 2011 via http://www.medicinescomplete.com/mc/stockley/current/interactions.htm?q=somatropin

Authors

Cathy Dewdney, Lead Pharmacist (Paediatrics), Great Western Hospitals NHS Foundation Trust.
Lisa King, Senior Formulary Pharmacist, Great Western Hospitals NHS Foundation Trust.

Date written

6th November 2011

Date of review

6th November 2013