Growth Hormone (Somatropin) in children and young people

Traffic light classification – Amber 1
Information sheet for Primary Care Prescribers

Indications

- Growth hormone deficiency (GHD), including acquired GH deficiency as the result of brain tumours, cranial irradiation or other brain injury, defined as a peak growth hormone of less than 6.7micrograms/L on two stimulation tests
- Turner syndrome (TS)
- Prader-Willi syndrome (PWS - licence also includes improvement of hypotonia and body composition)
- Chronic renal insufficiency (CRI)
- Children born small for gestational age (SGA) with subsequent growth failure at 4 years of age or later
- Short stature homeobox-containing gene (*SHOX*) deficiency

Any patient groups to be excluded from shared care

Any particular circumstances to be taken into account will be highlighted and where relevant patients will be excluded from shared care by specialists prior to initiation.
Groups that are excluded from shared care include:

- Patients ≥ 19 years old (traffic light classification – Red)
- Indications other than listed above

Therapeutic Summary

Human growth hormone is produced by the anterior pituitary gland. The synthetic form is called somatropin (recombinant human growth hormone). Human growth hormone is essential for normal growth in children. It 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. Human growth hormone also has important effects on the metabolism of proteins, lipids and carbohydrates, not only during childhood, but also throughout adult life. Growth failure in children can be a result of growth hormone deficiency (GHD), but also occurs in children with Turner Syndrome (TS), chronic renal insufficiency (CRI), short stature homeobox-containing gene (*SHOX*) deficiency, and in children born small for gestational age (SGA).
Somatropin (recombinant human growth hormone) is currently the only active treatment option for patients with these conditions.

Products available

First line products in Nottinghamshire are Omnitrope® (Sandoz), Humatrope® (Lilly), Genotropin® (Pharmacia) and Norditropin® (NovoNordisk)**-** Other brands may be used for existing patients, and those unable to tolerate or operate a first line brand device. **Second-line products** include Saizen® (Merck Serono) and Nutropin Aq® (Ipsen).

Growth Hormone (somatropin) should be PRESCRIBED BY BRAND to avoid substitution of similar products during dispensing. Not all products have marketing authorisations in the UK for all indications approved by NICE (see table below).
The choice of product should be made on an individual basis after informed discussion between the consultant 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.

The product licence for each manufacturer is as follows at time of ratification:

Product	GHD	TS	PWS	CRI	SGA	SHOX
Omnitrope®	✓	✓	✓	✓	✓	
Genotropin®	✓	✓	✓	✓	✓	
Humatrope®	✓	✓		✓	✓	✓
Norditropin®	✓	✓		✓	✓	
NutropinAq®	✓	✓		✓		
Saizen®	✓	✓		✓	✓	

Medicines Initiation
Growth hormone therapy for children and young people with growth failure will be initiated by the Paediatric Endocrine department at Nottingham Children's Hospital or under their instruction at a satellite service. Satellite services are provided by Lincoln County Hospital and Sherwood Forest Hospitals. The specialist nurse or homecare service will provide injection equipment and instruction in home injection technique. If your patient is not under homecare arrangements, please ensure they have appropriate administration equipment and disposal processes.

Homecare
Growth hormone is available through homecare. This service (comprising the delivery of medicine, ancillaries e.g. needles, sharps bin, waste collection and nurse training visit) is generally provided at no extra cost to the prescriber. The hospital will register patients with homecare service if this is the preferred delivery method chosen by the patient. One month homecare prescription will be issued from the hospital whilst the shared care is being arranged. Once this arrangement is agreed, the homecare provider will request further repeat prescription from the GP subsequently. To ensure treatment continuity, it is therefore vital that the GP responds to the shared care request letter sent by the hospital in a timely manner.

To ensure clinical governance around the homecare service, the Service Level Agreement (SLA) between the Trust and the homecare provider can be shared with the GP. A copy of the SLA can be requested by contacting the hospital's pharmacy homecare team (homecare@nuh.nhs.uk). Contact details for the various homecare providers are outlined in the SLA which should be used for any queries or complaints about the homecare service.

Occasionally, pharmaceutical companies may change their homecare provider. The hospital or the homecare provider will notify the GP if this occurs.

Dosages and route of administration
Growth Hormone is self-administered or given to the child by an adult as a once daily dose by subcutaneous injection. Dose is dependent upon indication and will be specified by the specialist, including any dose adjustments for height, weight and IGF-1 level changes over time.

Indication	Dose
GH deficiency	25 - 35micrograms/kg/day or 0.7 - 1mg/m^2/day
Turner syndrome	45 - 50 micrograms/kg/day or 1.4 mg/m^2/day
Chronic renal insufficiency	45 - 50 micrograms/kg/day or 1.4 mg/m^2/day
Prader-Willi syndrome	35 micrograms/kg/day or 1 mg/m^2/day (max 2.7mg daily)
SGA children	35 micrograms/kg/day or 1 mg/m^2/day
SHOX gene mutations	45 - 50 micrograms /kg/day or 1.4 mg/m^2/day

Contraindications
- Evidence of tumour activity (complete antitumour therapy and ensure intracranial lesions inactive before starting)
- Must not be used after renal transplantation or for growth promotion in children with closed epiphyses (or near closure in Prader-Willi syndrome)
- Severe obesity or severe respiratory impairment in Prader-Willi syndrome
- Growth hormone should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or to patients having acute respiratory failure

Pregnancy
Patients are advised to ensure effective contraception measures during growth hormone therapy. In the event of pregnancy occurring during growth hormone therapy the patient should be advised to discuss with the growth service immediately.

Precautions
- diabetes mellitus or its risk factors (adjustment of antidiabetic therapy may be necessary)
- papilloedema
- relative deficiencies of other pituitary hormones (notably hypothyroidism - manufacturers recommend periodic thyroid function tests but limited evidence of clinical value)
- history of malignant disease, increased risk of second neoplasm has been reported in patients treated with somatropin after certain first neoplasms.
- disorders of the epiphysis of the hip (slipped capital epiphyses, monitor for limping or knee pain)
- resolved intracranial hypertension (monitor closely)
- initiation of treatment close to puberty not recommended in child born small for gestational age
- Silver-Russell syndrome
- rotate subcutaneous injection sites to prevent lipoatrophy

Adverse Effects

- headache and/or visual problems (possibly due to idiopathic (benign) raised intracranial hypertension)
- nausea and vomiting
- fluid retention (peripheral oedema)
- arthralgia
- myalgia
- carpal tunnel syndrome
- paraesthesia
- antibody formation
- hypothyroidism
- insulin resistance
- hyperglycaemia
- hypoglycaemia
- reactions at injection site
- scoliosis
- gynaecomastia
- pancreatitis
- There is a theoretical risk that long-term high dosage GH treatment may increase the risk of malignancy, but extensive data collection from children and adolescents already treated for a primary tumour or leukaemia does not show an increased risk of secondary malignancy
- Children with GH deficiency may be at increased risk of Perthes disease during GH induced catch-up growth.
- Children with TS and PWS have increased susceptibility to diabetes mellitus.

For a full list of side effects refer to the BNF or Summary of Product Characteristics

Monitoring Requirements and Responsibilities

Pre-treatment assessment will be performed by the specialist and will include:

- growth monitoring, assessment of thyroid function, pubertal status, bone age and confirmation of underlying diagnosis (including growth hormone stimulation testing as necessary)

Ongoing monitoring: to be performed by the growth service who will monitor growth response at 3 to 6 monthly intervals
In addition the growth service will monitor the following as necessary:

- Thyroid function annually or when indicated.
- IGF1 levels annually and dose titrated accordingly
- Bone age assessment annually or when indicated (e.g. after dose changes)
- Assessment of pituitary status as other hormonal deficiencies may be unmasked by treatment with GH (if indicated).
- Sex hormone replacement to induce puberty at the normal timing if indicated.
- Examining patients with GHD secondary to an intracranial lesion for evidence of progression or recurrence of underlying disease

Discontinuation of Growth Hormone therapy will be the decision of the specialist team in line with current NICE Guidance (see references)

Young people seen by members of the Nottingham Paediatric Growth Service will be retested at final height to see if they fulfil the adult growth hormone eligibility criteria

as per NICE TA 2003. Those needing to continue with growth hormone therapy will be referred to the appropriate adult endocrinology service for their ongoing care.

Explicit criteria for review and discontinuation of the medicine

Severe or recurrent headaches	Perform urgent fundoscopy for papilloedema and discuss with growth hormone service if positive result
Visual disturbances	Perform urgent fundoscopy for papilloedema and discuss with growth hormone service if positive result
Nausea and vomiting	Perform urgent fundoscopy for papilloedema and discuss with growth hormone service if positive result
Peripheral oedema	Withhold and discuss with growth hormone service
Signs of hypothyroidism- lethargy etc	Discuss with growth hormone service
Injection site reactions	Vary injection site, if severe discuss with growth hormone service
Adherence issues	Discuss with growth hormone service

IF YOU ARE IN ANY DOUBT ABOUT ANY POTENTIAL ADVERSE REACTION, PLEASE CONTACT THE GROWTH SERVICE. THERE IS 24 HOUR CONSULTANT PAEDIATRIC ENDOCRINE ADVICE AVAILABLE THROUGH QMC SWITCHBOARD ON 0115 9249924 (ask to speak to the Paediatric Endocrinologist on call)

Clinically relevant medicine interactions and their management

Corticosteroids	growth-promoting effect of somatropin may be inhibited by corticosteroids – discuss with specialist team prior to initiation
Oestrogens	increased doses of somatropin may be needed when given with oestrogens (when used as oral replacement therapy) – discuss with specialist team prior to initiation
Drugs metabolised by cytochrome P 450 enzymes, particularly 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and ciclosporin)	Metabolism may be increased by growth hormone treatment, leading to lower plasma levels, clinical significance unknown – discuss with specialist team prior to initiation
Antidiabetic agents including insulin	Growth hormone treatment may cause hyperglycaemia and increase the risk of insulin resistance. – discuss with specialist team prior to initiation or dose adjustment

For a full list of drug interactions refer to the Summary of Product Characteristics

Information given to patient

Information will be provided to the patient on an individual basis, depending on the indication for the use of growth hormone and the brand of growth hormone selected. Age appropriate information sheets on a variety of paediatric endocrine problems can be found at https://www.eurospe.org/patients/english-information-booklets/.

Patient's roles and responsibilities

The patient or carer will report any symptoms suspected to be adverse reactions to the GP for assessment, particularly those possibly associated with benign intracranial hypertension – e.g. severe or recurrent headaches, visual disturbances, nausea and vomiting or peripheral oedema.

References

1. Humatrope 6mg, 12mg, or 24mg powder and solvent for solution for injection – Eli Lilly and Company Ltd. Summary of Product Characteristics [10-Aug-2021] on Electronic Medicines Compendium: (accessed on 17/02/2022) via www.medicines.org.uk/
2. Genotropin 5.3mg,or 12mg – Pharmacia. Summary of Product Characteristics [17-Jan-2022] on Electronic Medicines Compendium: (accessed on 17/02/2022) via www.medicines.org.uk/
3. Norditropin 5mg, 10m or 15mg – NovoNordisk Limited. Summary of product Characterisitcs [09 June 2021] on Electronic Medicines Compendium (accessed on 14/03/2022) via www.medicines.org.uk
4. NutropinAq 10mg/2ml – Ipsen Limited. Summary of Product Characteristics [30-Sep-2021] on Electronic Medicines Compendium: (accessed on 17/02/2022) via www.medicines.org.uk/
5. Saizen 8mg click.easy – Merck Serono. Summary of Product Characteristics [25-Jan-2022] on Electronic Medicines Compendium: (accessed on 17/02/2022) via www.medicines.org.uk/
6. Omnitrope 10mg/1.5ml solution for Injection – Sandoz Limited. Summary of Product Characteristics [11-Feb-2022] on Electronic Medicines Compendium: (accessed on 17/02/2022) via www.medicines.org.uk/
7. NICE TA 188: Human growth hormone (somatropin) for the treatment of growth failure in children (review) July 2010. available at www.nice.org.uk
8. BNF April 2013. Available from www.bnf.org [accessed 24/04/2013]
9. British Society for Paediatric Endocrinology and Diabetes (BSPED) Clinical Committee: Treatment of Children with Recombinant Growth Hormone: Shared Care Protocol 2015 available at: https://www.bsped.org.uk/media/1377/sharedcaregh_july2015.pdf
10. Baxter K (ed), *Stockley's Drug Interactions*. [online] London: Pharmaceutical Press accessed via www.medicinescomplete.com (accessed on 24/04/2013)
11. NICE TA 64: Human growth hormone (somatropin) in adults with growth hormone deficiency August 2003. available at www.nice.org.uk