HUMAN GROWTH HORMONE (SOMATROPIN) FOR TREATMENT OF GROWTH FAILURE IN CHILDREN PRESCRIBING SUPPORT INFORMATION

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 TA188: Human Growth Hormone (Somatropin) for treatment of growth failure in children
Somatropin is recommended as a treatment option for children with growth failure associated with any of the following conditions:
- Growth hormone deficiency (GHD)
- Turner syndrome (TS)
- Prader–Willi syndrome (PWS)
- Chronic renal insufficiency (CRI)
- Born small for gestational age with subsequent growth failure at four years of age or later (SGA)
- Short stature homeobox-containing gene deficiency (SHOXD).

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.

Indications for Treatment

Growth hormone deficiency causing short stature
- **Idiopathic isolated GH deficiency**
  - Growth disturbance in children due to insufficient secretion of growth hormone.
  - Growth Hormone deficiency as demonstrated biochemically on a provocation test, growth hormone level <8ug/l
- **Congenital hypopituitarism**
  - e.g. anomalies of the pituitary gland such as septo-optic dysplasia, and other pituitary hormone deficiencies
- **Acquired hypopituitarism**
  - e.g. craniopharyngioma & post cranial irradiation or neuro-surgery or traumatic brain injury

For conditions where there is a known cause, (e.g. CNS pathology or prior radiotherapy), one biochemical test to detect GH deficiency would suffice. The biochemical test should indicate growth
hormone levels below the lower cut off range for the local laboratory (8ug/l). For conditions where there is no known cause of growth hormone deficiency, biochemical evidence of growth hormone deficiency should be demonstrated on 2 separate occasions.

**Turner Syndrome** - confirmed by chromosome analysis

**Chronic renal failure**
- For the treatment of growth failure associated with this condition where renal function is decreased to less than 50%.

**SHOX deficiency** - confirmed by DNA analysis

**Prader-Willi syndrome confirmed by Chromosomal analysis OR Phenotype**
- Sleep studies will be performed prior to commencing growth hormone and repeated 3-4 months after starting treatment due to children with PWS have a high incidence of both central and obstructive apnoea.

**Small for Gestational Age (SGA)**
- All the following criteria must be met:
  - Over 4 years of age and a length or weight at birth that is 2 standard deviations below (−2 SD) the population average for birth length or weight.
  - Height SDS −2.5 and parental adjusted height SDS −1
  - No evidence of catch up growth by the age of 4 years

**Prescribing**

**When will GPs be asked to prescribe?**

**Funding approval process** - Clinicians will seek funding approval before commencing treatment using the standard group prior approval proforma.

GPs will only be asked to prescribe growth hormone once funding has been approved by CCG and once the patient has chosen the growth hormone device. Patient injection training will be undertaken by the Paediatric Endocrine Nurse Specialists, who will be able to offer on-going support to families during treatment. As per The East Of England Priority Advisory Committee ‘PAC’ guidance statement, any patient who chooses to use Norditropin SimpleXx the growth hormone prescriptions will be provided via secondary care.

**Preparations available**

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<thead>
<tr>
<th></th>
<th>Genotropin</th>
<th>- Genotropin Pen 5.3mg and 12mg</th>
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<tr>
<td></td>
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<td>- Go Quick pen 5.3mg and 12mg</td>
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<td>- MiniQuick In increments of 0.2mg</td>
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<tr>
<td>Norditropin</td>
<td>- Norditropin SimpleXx 5mg, 10mg and 15mg pens</td>
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<td>- Nordiflex</td>
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<td>Omnitrope</td>
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<td>Zomacton</td>
<td>- Zomaject 2 vision 4mg</td>
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<td>- Zomaject Vision X 10mg</td>
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<td>Saizen</td>
<td>- 6mg, 12mg and 20mg cartridges for use with the Easy Pod</td>
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<tr>
<td>Nutropin Aq</td>
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**Recommended Growth Hormone Preparations as per ‘PAC’ guidance statement**

The East of England Priorities Advisory Committee (PAC) have worked with clinical leads in the East of England to agree a list of recommended products for use in the majority of patients whilst still providing patient choice, and criteria for where the use of more expensive products can be justified.

**Group 1 products: Preferred products for use in the majority of patients**

These products provide a range of core features, are cost effective, and are the preferred products for use in the majority of patients. The rationale for product selection is outlined below:

- **Omnitrope products** (SurePal, Omnitrope Pen): Currently the least costly products.
- **Genotropin products** (Genotropin pen, GoQuick, Miniquick): These provide a range of devices including a pre-filled pen and a disposable device for travelling. The Miniquick can be stored out of the fridge for up to 6 months.
- **Norditropin SimpleXx and Nordiflex pre-filled pen**: Does not require fridge storage once in use and therefore is useful for children whose care is split between homes or whose lifestyle makes fridge storage difficult. Device has an auto needle inserter which helps to facilitate self-injection. This product is currently significantly more expensive in primary care and therefore, if chosen, prescribing should be retained in secondary care.
- **Humatrope** (HumatroPen) (for SHOX deficiency)

**Group 2 products: Products for use in patients with specific needs**

The following products are more costly options but have features that provide significant benefits to a cohort of patients: The rationale for product selection is outlined below:

- **Zomacton VisionX needle free**: Needle free device for use in patients with a confirmed needle phobia.
- **Saizen Easypod 3**: This is a larger device which may benefit patients who may have difficulty in handling the smaller devices. It allows monitoring of compliance and is lockable to prevent dose tampering so may be useful for patients where there are concerns around compliance and safety. The device has a hidden needle and auto inserter making the whole process invisible and which may be necessary to aid compliance in some patients. The Easypod can be kept out of the fridge for up to 7 days.

**Group 3 products: not for routine use:**

The following products are more costly options and do not offer significant advantages over preferred products in groups 1 & 2. The clinician should offer reasons for choosing group 3 products over products in groups 1 & 2.

- **NutropinAq pen**

**Dosage and Administration**

- **Growth Hormone Deficiency** 0.7 – 1.0 mg/m²/day or 23 – 39 micrograms/kg/day given as a daily subcutaneous injection.

- **Turners Syndrome** 1.4 mg/m²/day or 45-50 micrograms/kg/day given as a daily subcutaneous injection.
• **Chronic Renal Failure** 1.4 mg/m^2^/day or 45-50 micrograms/kg/day given as a daily subcutaneous injection.

• **SHOX** 1.4 mg/m^2^/day or 45-50 micrograms/kg/day given as a daily subcutaneous injection.

• **Prader-Willi syndrome** The starting dose is 3.5 mg/m2/week (0.5 mg/m2/day), increasing to 5 mg/m2/week (0.7 mg/m2/day) after 6 weeks and 7mg/m2/week (1 mg/m2/day) 12 weeks after commencing treatment; maximum dose 2.7mg daily given as a subcutaneous injection.

Only Genotropin® and Omnitrope® have been licensed for use in PWS.

NOTE - PWS patients appear to be highly sensitive in terms of IGF-1 generation, and standard GH doses often result in IGF-1 levels outside the normal range. The optimal management of these high IGF-1 levels is currently unclear. The potential risk needs to be balanced against the evidence that a dose of 1mg/m2/day is required for favourable effects on body composition.

• **Small for Gestational Age** 1.0 mg/m^2^/day or 0.035 micrograms/kg/day given as a daily subcutaneous dose.

**Treatment Stopping Criteria**

Treatment with somatropin should be discontinued if any of the following apply:

- Growth velocity increases less than 50% from baseline in the first year of treatment.
- Final height is approached and growth velocity is less than 2cm total growth in one year.
- There are insurmountable problems with adherence.
- Final height is attained.
- 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.

**INFORMATION FOR PRESCRIBING**

**Contraindications**

- avoid injections containing benzyl alcohol in neonates
- evidence of tumor activity (complete antitumor therapy and ensure intracranial lesions inactive before starting)
- not to be used after renal transplantation
- not to be used for growth promotion in children with closed epiphyses (or near closure in Prader-Willi syndrome)
- severe obesity in Prader-Willi syndrome
- severe respiratory impairment in Prader-Willi syndrome

**Cautions**

- Diabetes mellitus (adjusting of antidiabetic therapy may be necessary)
- Disorders of the epiphysis of the hip (monitor of limping)
- History of malignant disease
- Hypothyroidism
- initiation of treatment close to puberty not recommended in child born small for corrected gestational age;
• Papilledema
• Resolved intracranial hypertension (monitor closely)
• Silver-Russell syndrome

What are the main side-effects?
• The safety record is excellent. No serious side effects have been recognised to date. There is no possibility of contamination with a slow virus as occurred with preparations of pituitary-derived growth hormone.
• 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, hyperglycaemia, hypoglycaemia) but international studies have shown that the incidence of permanent diabetes is not increased with treatment.
• Extensive surveys have failed to demonstrate an increase in any form of malignant disease. Some children selected to receive GH will have had cancer and may be at risk of primary tumour recurrence or a secondary tumour; no increased risk of such events has been demonstrated with growth hormone treatment.

Drug Interactions
• Growth promoting effect may be inhibited when combined with corticosteroids.
• Increased doses of GH may be required if on oestrogen replacement therapy.
• Anti-diabetic therapy may require adjustment.

Monitoring

Biosynthetic human growth hormone has a good safety record and frequent monitoring is not required. Monitoring is performed in secondary care only.

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References
NICE technology appraisal guidance [TA188]. Published date: May 2010. Human growth hormone (somatropin) for the treatment of growth failure in children. [https://www.nice.org.uk/guidance/ta188](https://www.nice.org.uk/guidance/ta188)

BNF online [www.medicinescomplete.com](http://www.medicinescomplete.com)

Document Management

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