Shared Care Guideline for Recombinant Growth Hormone in Children.

Somatropin (recombinant growth hormone – r-hGH)

Executive Summary/ Critical Information.

Indication*	Route & Dose	Key aims of treatment in the long term	Monitoring undertaken by specialist before requesting shared care	Ongoing monitoring to be undertaken by GP	Duration of treatment	Stopping criteria	Follow up (weeks/months)
For the treatment of growth failure in children associated with SHOX, GHD, SGA, CKD, PWS and TS. NICE TA188	Subcutaneous injection, variable dose per patient	GHD : achievement of genetic potential SHOX/SGA/ CKD: increase of final height PWS: improvement of body composition	Baseline, height, weight and IGF-1 levels, pubertal development Bone age	Prescribing continued by GP after one month; occasional support with height assessment and adherence may be requested by specialist team.	Completion of puberty (menarche for females and testicular volume 20-25mL for males) and termination of linear growth (height velocity <2cm/year), or poor response to treatment	1. Poor response: growth velocity <50% from baseline in first year of treatment; 2. final height attained: growth velocity <2cm total growth in 1 year; 3. Poor adherence	Specialist - 4-6 monthly (months) GP – In accordance with prescription requirements and occasional support requested by specialist team.

Key Safety Notice (for instance: notification if prescribing must be brand specific or BNF cautionary and advisory warnings).

Brand and device specific as per patient preference and product licensing.

In general r-hGH has an excellent safety record; although antibody formation can be detected, this is rarely of physiological relevance.

*Abbreviations: Growth hormone deficiency (GHD); Turner syndrome (TS); Prader–Willi syndrome (PWS); Chronic Kidney Disease (CKD); Small for gestational age (SGA); Short stature homeobox-containing gene deficiency (SHOX).

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1. Background

Somatropin, also known as recombinant human growth hormone (r-hGH) has a sequence identical to natural human growth hormone (GH) and has been used in the UK since 1985.

Somatropin is a peptide hormone that stimulates growth, cell reproduction and regeneration in humans and other animals. It is a type of mitogen which is specific only to certain kinds of cells. Growth hormone is a 191-amino acid, single-chain polypeptide that is synthesized, stored, and secreted by somatotropic cells within the lateral wings of the anterior pituitary gland. GH is a stress hormone that raises the concentration of glucose and breaks down fat. It also stimulates production of IGF-1.

The early recognition of growth failure is an essential component of a national strategy leading to rational and effective use of r-hGH. Monitoring of growth (height & weight) should be part of all childhood health surveillance in primary care and in school.

The diagnosis of GH deficiency (GHD) is based on a combination of the following:

1. Short stature that is inappropriate for the parental height.
2. Subnormal growth rate: i.e. height velocity below 25th centile.
3. Association with other pituitary hormones deficiency, as in multiple pituitary hormone deficiency.
4. Growth delay confirmed by delayed skeletal maturation (bone age).
5. Clinical and/or imaging evidence of a structural disorder of the hypothalamo-pituitary axis; this includes previous cranial irradiation.
6. Exclusion of other genetic, psychosocial and systemic causes of growth failure.
7. Biochemical evidence of GHD to provocation testing. Consideration should be given to neurosecretory dysfunction of GH release where provocation testing may reveal a normal response but other evidence suggests a diagnosis of GHD.

Use of somatropin is recommended for these indications under the Nice Institute for Clinical Excellence (NICE) technology appraisal guidance (May 2010) 'Human growth hormone (somatropin) for the treatment of growth failure in children' and prescribing should be kept in line with NICE guidance. It is recommended in this guidance that treatment should be initiated and monitored by a paediatrician with expertise in managing growth-hormone disorders and that treatment can be continued under a shared-care protocol by a general practitioner.

Treatment with r-hGH should always be initiated and monitored by a specialist (Consultant Paediatric Endocrinologist or Consultant Paediatrician with expertise in growth disorders).

2. Important information

Treatment with r-hGH will be discontinued if the following occur:

1. Poor response:
    a. Increase in growth velocity less than 50% in first year of therapy
    b. Final height is approached and growth velocity is <2 cm total growth in 1 year
2. Poor adherence
3. Final height is attained
4. Completion of puberty and termination of linear growth (Turner syndrome and Prader Willi syndrome)

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Patients with GH deficiency are transferred to the adult endocrine clinic at St Bartholomew's hospital after completion of growth. An insulin tolerance test will be arranged to re-assess GH secretion. If this shows subnormal GH secretion, follow-up will continue in the adult clinic, where their care will be transferred to the adult endocrinologists.

3. Drug name, form, and licensed indications (unlicensed/off-label)

Somatropin is administered as a subcutaneous injection, or needle transjection, once daily. Depending on the brand, injections may be prepared from multi-dose ampoules or by using cartridges in a multi-dose pen injection device or other disposable devices.

Training will be delivered by clinical nurse specialist at the hospital or a homecare nurse in the child's home (arranged by the clinical specialist nurse). Either the child or parent/guardian will give the first and all subsequent injections at home. The injection site should be rotated to avoid lipoatrophy.

There are several products for patients and parents to choose from, and the choice of product is based on patient preference. The current brands of somatropin are:

- Genotropin
- Humatrope
- Norditropin NordiFlex
- Norditropin Flexpro
- Nutropin Aq
- Omnitrope
- Saizen

The licensed indications for treatment with r-hGH are:

1. Growth failure due to GH deficiency:
    1. Idiopathic isolated GHD
    2. Congenital hypopituitarism e.g. anomalies of the pituitary gland such as septo-optic dysplasia.
    3. Acquired hypopituitarism e.g. craniopharyngioma, post cranial irradiation, neuro-surgery or traumatic brain injury
2. Short stature in children with Turner syndrome (confirmed by chromosome analysis).
3. Growth retardation in pre-pubertal children with chronic renal failure (CRF).
4. Abnormal growth and body composition in children with Prader-Willi syndrome (confirmed by chromosome analysis).
5. Growth failure in children born Small for Gestational Age (SGA) (defined as birth length SDS <-2 or birth weight SDS <-2):
    - Growth disturbance (current height SDS <-2.5 and parental adjusted height SDS <-1) in short children born SGA who fail to show catch up growth by 4 years (as recommended by NICE).
6. Growth failure associated with SHOX deficiency (confirmed by DNA analysis).

Somatropin (Growth Hormone) Cost in Primary Care for Brands and Preparations available in the UK

Company	Brand	Presentation	Strengths of Presentation (mg)	Primary Care Cost (per mg of somatropin)
Pfizer	**Genotropin®**	Pen Cartridge	5.3mg and 12.0mg	£17.38
		GoQuick® prefilled multi -dose pen	5.3mg and 12.0mg	
		MiniQuick® single dose syringes	0.2mg up to 2mg (in increments of 0.2mg)	
Sandoz	**Omnitrope®**	"Surepal" Pen Cartridge	5mg, 10mg and 15mg	£17.35
Eli Lilly	**Humatrope®**	Pen Cartridge	6mg, 12mg and 24mg	£18.00
Ipsen	**Nutropin Aq®**	Pen Cartridge	10mg	£20.30
Novo Nordisk	**Norditropin®**	Flexpro® prefilled multi -dose pen	5mg, 10mg and 15mg	£23.18
		Nordiflex® prefilled multi -dose pen	5mg, 10mg and 15mg	£23.18
Merck Sereno	**Saizen®**	Pen Cartridge	6mg, 12mg and 20mg	£22.87
Prices accessed from BNF April 2021				

Growth hormone dosage (calculated in mg/kg/day or mg/m^2/week in divided doses)

Indication	Licensed product	Dose - mg/kg/day	Dose – mg/m^2/week
Growth Hormone Deficiency (GHD)	All	0.025mg – 0.035mg	5-7 mg
Turner Syndrome	All	0.045-0.05mg	10mg
Chronic Renal Failure	All	0.045 – 0.05mg	10mg
Prader-willi Syndrome	Only Omnitrope®	0.035mg	7.5mg (max 2.7mg/day)
Small for Gestational Age (SGA)	All except NutropinAq®	0.035mg	7.5mg
SHOX deficiency	Humatrope® **and** Genotropin®	0.045 – 0.05mg	10mg
(Doses formerly expressed in units: 3 units = 1 mg. doses for mg/m^2 may be lower than mg/kg in obsese children			

4. Contraindications/Cautions

Contra-indications:

- Evidence of tumour activity (complete anti-tumour treatment and ensure intracranial lesions inactive before starting) (BNF).

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- Closed epiphyses.
- Post renal transplantation
- Severe respiratory impairment in Prader-Willi syndrome

Cautions:

- In diabetic patients, insulin dose may need to be adjusted on GH initiation
- Thyroid tests recommended
- Disorders of epiphysis of the hip- monitor for limping.
- May increase clearance of drugs metabolised by cytochrome p450 3A4 e.g. anticonvulsants and cyclosporin.
- Corticosteroids may inhibit growth promoting effects of somatropin
- Higher doses of somatropin may be needed with oral oestrogen replacement therapy.
- PWS patients with the following risk factors:
    1. Severe obesity
    2. History of respiratory impairment or sleep apnoea
    3. Unidentified respiratory infection

Must be referred to a paediatric respiratory physician for evaluation of upper airway obstruction before initiation of treatment with growth hormone. If there are signs of upper airway obstruction treatment should be ceased and referred again for a paediatric respiratory physician for evaluation

Risk of Neoplasia:

Extensive surveys have **not** suggested any increased risk of tumours or leukaemia with r-hGH therapy compared with similar patients who have not received therapy when replacement doses are physiological in confirmed GHD. Supra-physiological doses have not been assessed. Concern has been expressed following a report from the UK that young adults treated with human pituitary GH up until 1985 had a higher mortality risk for colon cancer and non Hodgkin lymphoma than the general population (Swerdlow AJ et al, Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959-85: a cohort study. Lancet 2002; 360: 273-7). However, these data were collected on patients on high doses of human pituitary derived GH which may have also contained other growth factors. Although these data raise concern, **they do not provide firm evidence of an association**. Long-term surveillance of patients receiving r-hGH therapy irrespective of diagnosis is continuing through National Cancer Registries.

Prader Willi Syndrome (PWS):

PWS is a rare genetic disorder. In the first year of life it is characterised by hypotonia and failure to thrive, but in later years severe obesity may ensue. These children usually have short stature, which is now generally accepted to be associated with GHD. Randomised controlled studies of r-hGH in PWS have demonstrated an increase in short term linear growth analogous to that seen in patients with GHD. The r-hGH dosing schedule is similar to that used in GHD. Data on final heights are now becoming available and are similar to those observed in GHD patients. Although the value of increasing the stature of these individuals can be questioned, the effect of r-hGH treatment on body composition is of greater importance. r-hGH therapy leads to a decrease in fat mass and an increase in lean body mass. The latter is less obvious in PWS but is in contrast to the reports of increased muscle strength and agility. The observation of improved respiratory muscle function is of particular importance in these individuals. To date the safety profile of growth hormone in PWS is similar to that observed in the GHD child. However, in severely obese patients with PWS and those with sleep apnoea, careful consideration needs to be given to r-hGH as potential risk of sudden death has been reported although not necessarily linked to sleep apnoea. Sleep studies and ENT opinions are now recommended prior to commencement of r-hGH therapy in children with PWS.

5. Drug interactions

There are no significant interactions with somatropin.

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For complete list of side effects, please refer to the SPC: https://www.medicines.org.uk/emc.

6. Side effects which require managing

Adverse effects	Symptoms/signs	Actions
Transient local skin reactions at injection site	Redness, inflammation	Rotate injection sites
Fluid retention, uncommon in children. More common in Turner Syndrome	Peripheral oedema	May subside spontaneously or dose reduction may be required - discuss with endocrine consultant
Arthralgia	Pain in joints	Start appropriate analgesia
Myalgia; may be related to the preservative m-cresol, a preparation without this preservative can be substituted	Pain or inflammation of voluntary muscle	
Hypoglycaemia/ Hyperglycaemia	Hypoglycaemia: hunger, nausea, sweating, weakness, faintness, confusion, hallucinations, headache, cold sweat, piloerection, hypothermia, irritability, bizarre behaviour and fainting Hyperglycaemia: thirst, polyuria, tiredness, unintentional weight loss, and increased susceptibility to infections	Check blood glucose and if BM <3.5 or > 8 mmol/L refer to Consultant Endocrinologist.
Benign intracranial hypertension	Severe/recurrent headache, visual problems, nausea/vomiting	Stop treatment immediately and urgently discuss with Consultant Endocrinologist, fundoscopy for papilloedema is recommended.
Slipped upper femoral epiphysis	Pain in hip, limp	Stop treatment, urgently discuss with Consultant Endocrinologist with the aim to seek same day orthopaedic review and opinion.

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7. Monitoring and Responsibilities

Baseline	• Accurate auxology: calculation of height velocity, height SDS or centile position, calculation of the parents mid-parental height, bone age, weight, body mass index, BMI SDS • Basal blood work-up: FBC, ESR, U&Es, LFTs, bone profile, celiac screen, TFT's, cortisol, IGF-1, Prolactin • Nutritional status with exclusion of coeliac disease • Karyotype if female, tests for PWS and Noonan's syndrome if necessary • Growth hormone provocation (not needed for Turner syndrome, small for gestational age, Prader-Willi syndrome and chronic renal failure) • Pubertal status	
Monitoring	At 4 months, then 4-6 monthly	• Auxology; to include height and height velocity, sitting height and weight • Pubertal status at appropriate age
	Annually	• IGF-1, TFTs, bone age every 1-3 years

a. Hospital specialist:

- Ensure that the patient/carer is an informed recipient in therapy.
- Ensure that patients understand their treatment regimen and any monitoring or follow up that is required (using advocacy if appropriate). Issue any local patient information leaflets where appropriate.
- Ensure baseline investigations are appropriate before commencing treatment. Give the patient a patient held booklet for result monitoring if appropriate.
- Ensure that a baseline height is available within 4 weeks before start of GH treatment
- Growth hormone should only be initiated in secondary care. When initiated in secondary care prescribe for one month. Send a letter to the GP requesting shared care for this patient.
- Clinical and laboratory supervision of the patient by blood monitoring and routine clinic follow-up on a regular basis.
- Responsible for overseeing brand and dose changes.
- Send a letter/results notification to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated.
- Evaluation of any reported adverse effects by GP or patient.
- Advise GP on review, duration or discontinuation of treatment where necessary.
- Inform GP of patients who do not attend clinic appointments.
- Ensure that backup advice is available at all times

b. General Practitioner:

- Outline the appropriate level and method (face-to-face or telephone consultation) of contact to be carried out with the patients to ensure clinical stability.
- Growth hormone should only be initiated in secondary care. Ensure patient is an informed recipient of therapy and baseline investigations are appropriate before continuing treatment.
- Where prescribing of somatropin is transferred to the GP, the community pharmacy will be dispensing and the hospital must ensure that the patient is supplied with the pens where required as they are not prescribable on the NHS. Where BD needles are compatible with the pen, these are prescribable on the NHS.

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- Check and reinforce patient understanding of the nature, effect and potential side effects of the drug before prescribing it and contact the specialist for clarification where appropriate
- To prescribe r-hGH as advised by the supervising Consultant and, where local practice dictates, discuss with the local Prescribing Advisor; feedback to the consultant any concerns regarding r-hGH prescribing and/or shared care.
- To monitor patient's overall health and well-being.
- To report any adverse effects of therapy to the supervising Consultant or deputy.
- Help in monitoring the progression of disease
- Discontinuation of growth hormone should only be decided by paediatric /adult endocrinologist (NICE guidelines)
- Ensure the patient is regularly attending hospital appointments whist receiving regular GH therapy

c. Patient or parent/carer:

- To ensure they have clear understanding of the prescribed treatment.
- To administer the r-hGH as directed by the supervising Consultant; attend clinic reviews as requested.
- Report any adverse effects to their GP and/or specialist
- Ensure they have a clear understanding of their treatment.
- Report any changes in disease symptoms to GP and/or specialist
- Alert GP and/or specialist of any changes of circumstance which could affect management of disease
- Undertake any monitoring as requested by the GP and/or specialist
- Report any adverse effects to their GP and/or specialist

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8. Contact Information

Paediatric Endocrine Consultants	Direct line (secretaries) 020 3594 0418 or 020 3594 2481 Via switchboard: 'consultant on call for paediatric diabetes and endocrinology'
Paediatric Endocrine Specialist Registrar	Bleep 1147 via switchboard 020 3416 5000
Paediatric Endocrine SHO	Bleep 1102 via switchboard 020 3416 5000
Paediatric Endocrine Clinical Nurse Specialists	Direct line 020 3594 1548
Hospital Pharmacist (where appropriate)	Direct line 020 3246 0133 Bleep 1063 via switchboard 020 3416 5000 ext 60133
Medicines Information Pharmacist	0203 416 5000 ext 60120

9. Document Management

Document ratification and history	
Produced by:	Laura Mattis, Specialist Paediatric pharmacist Lee Martin, Specialist Clinical Pharmacist Evelien Gevers, Consultant Paediatrician in Endocrinology and Diabetes
Approved by:	Waltham Forest and East London Medicines Optimisation and Commissioning Committee (WELMOCC)
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Appendix 1.

Shared Care Guideline: Prescribing Agreement

Section A: To be completed by the hospital consultant initiating the treatment

GP Practice Details:	**Patient Details:**
Name:	Name:
Tel No:	DOB:
Email (nhs.net):	NHS Number (10 digits):

Consultant Details:
Consultant Name:
Secretary Contact Details:
Tel No:
Email (nhs.net):

Diagnosis:	**Drug Name (to be prescribed by GP):** **Dose:** **Frequency:**

I will review the patient in clinic in weeks / months (*Delete as appropriate)*.

Dear

Your patient started treatment with the above drug for the above diagnosis on (insert date) and in my view; his/her condition is now stable.

The patient has given consent to treatment under a shared care prescribing agreement and has agreed to comply with instructions and follow up requirements.

I am requesting your agreement to sharing the care of this patient from (insert date) in accordance with the attached Shared Care Prescribing Guideline.

This patient was reviewed on (insert date). These are the results relevant for the drug and/or condition, as outlined in the shared care document:

Test	Baseline	Date

Please continue to monitor the patient as outlined in the shared care guidelines. Refer to the attached guidelines for monitoring criteria.

Other relevant information:

Consultant Signature:	Date:

Section B: To be completed by the GP and returned to the hospital consultant as detailed in Section A above [If returned via e-mail, use NHS.net email account ONLY]

Please sign and return your agreement to shared care within 14 days of receiving this request.

☐ Yes, I accept sharing care as per shared care prescribing guideline.

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☐ No, I am not willing to undertake shared care for this patient for the following reason: (Please give reason)		
GP Name:	GP Signature:	Date:

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