PATHWAYS AND GUIDELINES DEVELOPMENT SUBGROUP

Shared Care Protocol

GMMMG NHS

Shared Care Guideline for Growth Hormone in Adults		Reference Number
Version: 2	**Replaces: 1.2**	**Issue date:** 17/08/2017
Author(s)/Originator(s): (please state author name and department) Pennine Acute Hospitals NHS Trust		**To be read in conjunction with the following documents:** Current Summary of Product characteristics (http://www.medicines.org.uk) BNF online via https://www.medicinescomplete.com, NICE TA64 guidance - Human growth hormone (somatropin) in adults with growth hormone deficiency via http://www.nice.org.uk/guidance/ta64
Date approved by Pathways and Guidelines Development Subgroup: 13/07/2017	**Date approved by Greater Manchester Medicines Management Group:** 17/08/2017	
Date approved by Commissioners: *dd/mm/yyyy*	**Review Date:** 17/08/2019	

Please complete all sections

1. Name of Drug, Brand Name, Form and Strength	Somatropin (see section 6)
2. Licensed Indications	Recombinant human growth hormone (Somatropin) treatment is recommended for the treatment of adults with severe growth hormone (GH) deficiency that is severely affecting their quality of life and they fulfill all three of the following NICE criteria (TA 64, August 2003): • They have severe growth hormone deficiency (GHD), 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. • They have an 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.

	Patients who develop GHD in early adulthood, after linear growth is completed but before the age of 25 years, should be given somatropin until adult peak bone mass has been achieved, provided they satisfy the biochemical criteria for severe GHD as mentioned above. After the adult peak bone mass has been achieved, the decision to continue somatropin treatment should be based on all of the aforementioned three criteria. Nine months after initiation of therapy (an initial 3-month period of somatropin dose titration, followed by a 6-month therapeutic trial period) and ongoing monitoring, patients are reassessed and somatropin is only continued in those patients who demonstrate a QoL improvement of more than 7 points in the AGHDA score. These shared care guidelines are devised to support continuation of somatropin by the GP after the first nine months of therapy.
3. Criteria for shared care	Prescribing responsibility will only be transferred when: • Treatment is for a specified indication. • Treatment has been initiated and established by the secondary care specialist for 9 months. • The patient's initial reaction to and progress on the drug is satisfactory after 9 months demonstrating a QoL improvement of more than 7 points in the AGHDA score. • The GP has agreed in writing in each individual case that shared care is appropriate. • The patient's general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements
4. Patients excluded from shared care	• Unstable disease state. • Patient does not consent to shared care. • Patient does not meet criteria for shared care specified in section 3.
5. Therapeutic use & background	The prevalence of adult onset GH deficiency (GHD) is approximately 1 in 10,000 of adult UK population. 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. The majority of adult patients with adult onset GHD have a pituitary adenoma or hypothalamic tumour or have received treatment for such a lesion with surgery and/or irradiation. In addition there are patients who had GHD diagnosed during childhood. In these patients GHD may be idiopathic or may be a consequence of a hypothalamic tumour or may follow cranial irradiation for treatment of a cranial malignancy. The majority of adults with GH deficiency are both physically and psychologically compromised and report a poor quality of life. GH deficiency in adults may be associated with the following adverse features to a variable degree in any individual: body composition is altered (reduced lean mass and increased fat mass, especially in the trunk); osteopenia/osteoporosis (reduced 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 extra-cellular fluid volume; increased thickness of the intima media of blood vessels; and impaired cardiac function.
6. Contraindications (please note this does not replace the SPC or BNF and should be read in conjunction with it).	• Hypersensitivity to somatropin or any excipient of the formulation chosen. • Any evidence of active malignant tumours. Intracranial neoplasm must be inactive and antitumor therapy should be completed prior to institution of therapy. • 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 somatropin.

	• After renal transplantation. • Severe obesity or severe respiratory impairment in Prader-Willi syndrome. • GH treatment is contraindicated during pregnancy and lactation.
7. Prescribing in pregnancy and lactation	Pregnancy: Somatropin containing products should be discontinued if pregnancy occurs and are not recommended in woman of childbearing age not using contraception. Lactation: There have been no clinical studies conducted with somatropin in breastfeeding women. It is not known whether somatropin is excreted in human breast milk and therefore should be avoided whilst breast feeding.
8. Dosage regimen for continuing care	***Route of administration:*** Subcutaneous self administration
	Preparations available: Genotropin: powder and solvent: 5.3mg and 12mg powder and solvent miniquick: 0.2 mg,0.4 mg,0.6 mg,0.8 mg,1.0 mg,1.2 mg,1.4 mg,1.6 mg,1.8 mg, 2.0 mg Norditropin: Simplexx injection: 5mg/1.5ml, 10mg/1.5ml, 15mg/1.5ml NordiFlex: 15mg/1.5ml NutropinAq: 10mg/2ml Saizen: Solution for injection: (5.83mg/ml, 8mg/ml) powder for reconstitution: 8mg Click.easy
	Please prescribe: Treatment is self-administered by a daily subcutaneous injection. Initial dose of 0.15 – 0.3 mg daily, gradually increased if required to maximum 1 mg daily; use minimum effective dose (requirements may decrease with age). 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 maintenance dose in these patients seldom exceeds 0.5 mg per day.
	Is titration required: Yes, an initial 3-month period of somatropin dose titration, followed by a 6-month therapeutic trial period by the Consultant. Patients will only be transferred to GP after this.
	Adjunctive treatment regime: Nil
	Conditions requiring dose reduction: Dose reduction might be required if the patient develops: Fluid retention, arthalgia, and symptoms of carpal tunnel syndrome. Somatropin is metabolised within the liver and kidneys and excreted in bile however there are no data to suggest the need to reduce the dose in reduced hepatic and/or renal function.

Usual response time :
Titration of the dose takes 3-4 months.

Duration of treatment:
Continuation of therapy is only indicated if there is a satisfactory effect on patient quality of life after nine months of treatment, as defined by NICE TA64.
Shared care should not be sought until continuation of therapy has been confirmed. This 9 month assessment should be carried out by a Consultant Endocrinologist with a special interest in the management of growth hormone disorders prior to the maintenance treatment being prescribed under a shared care agreement

Treatment to be terminated by:
Consultant Endocrinologist or after discussion with Consultant Endocrinologist only.
Will be documented in medical notes, and communicated to GP via letter.

NB. All dose adjustments will be the responsibility of the initiating specialist care unless directions have been specified in the medical letter to the GP.

9.Drug Interactions

For a comprehensive list consult the BNF or Summary of Product Characteristics

The following drugs must <u>not</u> be prescribed without consultation with the specialist:

Corticosteroids: Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of somatropin containing products. Patients with ACTH deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on growth hormone.

The following drugs may be prescribed with caution:

Somatropin is predicted to increase the clearance of drugs metabolised by CYP3A4 and could potentially result in lower plasma levels of drugs such anticonvulsants, sex hormones and ciclosporin.
Somatropin may reduce the efficacy of insulin. For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin therapy is instituted.

Manufacturers state that monitoring is advisable.

10. Adverse drug reactions

For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event uncertain, consult Summary of Product Characteristics or BNF

Specialist to detail below the action to be taken upon occurrence of a particular adverse event as appropriate. Most serious toxicity is seen with long-term use and may therefore present first to GPs.

Side effects may include headache, arthralgia, myalgia, fluid retention, mild hypertension, carpal tunnel syndrome, visual problems, nausea and vomiting, paraesthesia, antibody formation, and reaction at the injection site. Benign intracranial hypertension is a rare complication.

Adverse event System – symptom/sign	**Action to be taken** Include whether drug should be stopped prior to contacting secondary care specialist	**By whom**
Headache: If severe, recurrent, or associated with nausea and vomiting.	Report immediately to the Specialist Endocrine Department. GH to be discontinued.	GP or Named Specialist Endocrinologist/Endocrinology Team

Signs of fluid retention: Such as peripheral oedema, stiffness in the extremities, arthralgia, myalgia and paraesthesia are common when starting somatropin	Usually mild to moderate and subsides spontaneously or with dose reduction. Discuss if persistent or severe paraesthesia present. Dose reduction may be necessary to avoid the development of carpal tunnel syndrome.	Named Specialist Endocrinologist/ Endocrinology Team
Lipoatrophy: May occur at site of injection	This can be avoided by varying the site of administration.	Patient to be educated on this aspect at the time of GH initiation by the Specialist Endocrinology Team
Insulin resistance: Diabetic patients on insulin may require increased insulin requirements	HbA1c should be monitored and patients advised accordingly	Named specialist Endocrinologist/ Endocrinology & Diabetes team.
Hypothyroidism: Has been observed with somatropin	Thyroid function should be monitored	Named specialist Endocrinologist/ Endocrinology team

The patient should be advised to report any of the following signs or symptoms to their GP without delay:

Severe recurrent headache associated with nausea and vomiting.

Other important co morbidities:

Retinopathy: In case of development of preproliferative changes and the presence of proliferative retinopathy somatropin replacement therapy should be discontinued. Stable background retinopathy should not lead to discontinuation of somatropin replacement therapy.

Leukaemia: Leukaemia has been reported in a small number of growth hormone deficiency patients, some of whom have been treated with somatropin. However, there is no evidence that leukaemia incidence is increased in growth hormone recipients without predisposing factors.

Any adverse reaction to a black triangle drug or serious reaction to an established drug should be reported to the MHRA via the "Yellow Card" scheme.

<table>
<tr><td>11. Baseline investigations</td><td colspan="2">Within Secondary Care:

Baseline
• Assess the patient & establish the need for Growth Hormone with provision of appropriate information on GHD and its treatment.
• Initiation of treatment and titration of dose based on IGF-1 levels including review of patient at monthly intervals for first three months.

Monitoring
• Assessment of quality of life by disease specific questionnaire (QoL- AGHDA) at 9 months
• Clinical & laboratory supervision of patient at 6-12 monthly intervals, including assessment of Weight (BMI), blood pressure, HbA1c, Thyroid Function Tests (TFTs), Lipid profile, IGF-1, clinical assessment of general health while patient remains on GH.</td></tr>
<tr><td>12. Ongoing monitoring requirements to be undertaken by GP</td><td>Is monitoring required?</td><td>No

As specified in section 11, the clinical and laboratory supervision will take place in secondary care at 6-12 monthly intervals but on occasions, if an interim clinical or biochemical parameter monitoring (such as check of blood pressure; HBA1C; TFTs; Lipid Profile) is required, then patient’s GP might be requested for the tests to be carried out in primary care by the Endocrinologist / Endocrinology team responsible for the patient.

Refer to above table in section 10 for monitoring of side-effects.</td></tr>
<tr><td>13. Pharmaceutical aspects</td><td colspan="2">Genotropin:
powder and solvent: 5.3mg and 12mg powder and solvent
Keep the two-chamber cartridge/pre-filled pen in the outer carton in order to protect from light. Do not freeze.
Before reconstitution:
Store in a refrigerator (2°C - 8°C), can be stored for a maximum of 1 month at or below 25°C.
After reconstitution:
From a microbiological point of view, once reconstituted, the product may be stored for 4 weeks at 2°C - 8°C.

Norditropin:
Simplexx injection: 5mg/1.5ml, 10mg/1.5ml, 15mg/1.5ml
Before use: Store in a refrigerator (2°C–8°C) in the outer carton, in order to protect from light. Do not freeze.
When in use, the product may be stored for a maximum of 28 days in a refrigerator (2°C–8°C), alternatively stored for a maximum of 21 days below 25°C. Store in the pen (NordiPen) during use. Do not freeze.

NutropinAq:
10mg/2ml
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the blister in the outer carton
Chemical and physical in-use stability has been demonstrated for 28 days at 2°C - 8°C.</td></tr>
</table>

	Saizen: Solution for injection: (5.83mg/ml, 8mg/ml) Store in a refrigerator (2°C-8°C). Do not freeze. Store in the original package to protect from light. When containing a cartridge of Saizen, the easypod auto-injector has to be stored in a refrigerator (2°C-8°C). When using the cool.click needle-free auto-injectors, only the cartridge of Saizen should be stored in a refrigerator (2°C-8°C). Chemical and physical in use stability has been demonstrated for 28 days at 5±3°C. From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 2°C to 8°C. powder for reconstitution: 8mg Click.easy Do not store above 25°C. Do not freeze. Store in the original package. After reconstitution, the product must be stored for a maximum of 28 days in a refrigerator (2°C-8°C). When containing a cartridge of reconstituted Saizen, the easypod and one.click auto-injectors have to be stored in a refrigerator (2°C-8°C). When using the cool.click needle-free auto-injectors, only the cartridge of reconstituted Saizen should be stored in a refrigerator (2°C-8°C).
14. Responsibilities of initiating specialist	• Diagnose • Initiate treatment and stabilised therapy for the first 9 months. • Undertake baseline monitoring • To assess and monitor patient's response to treatment, adjust somatropin dose accordingly and perform on-going monitoring • Follow up nine months after initiation of therapy (an initial 3-month period of somatropin dose titration, followed by a 6-month therapeutic trial period) to ensure patient's initial reaction to and progress on the drug is satisfactory demonstrating a QoL improvement of more than 7 points in the AGHDA score. • Follow up every 6-12 months to ensure continuing benefit of somatropin and carry out required monitoring sharing the results with the GP. • Ensure that the patient has an adequate supply of medication until GP supply can be arranged • Ensure patient suitability as per section 3 above • The consultant team will write formally to the GP to request shared care using the GMMMG agreed process. Failure to supply all the required information will result in the refusal of the request until all information has been supplied • Patients will only be transferred to the GP once the GP has agreed. • Continue to monitor and supervise the patient according to this protocol, while the patient remains on this drug, and agree to review the patient promptly if contacted by the GP • Provide GP with diagnosis, relevant clinical information and baseline results, treatment to date and treatment plan, duration of treatment before consultant review • Provide GP with details of outpatient consultations, ideally within 14 days of seeing the patient or inform GP if the patient does not attend appointment • To stop the drug or provide GP with advice on when to stop this drug • Provide patient/carer with relevant information to enable informed consent to therapy and to share care with the GP • The consultant team will ensure the patient/carer has been fully counselled on the benefits of somatotropin, the monitoring requirements and what will happen if the patient fails to attend for monitoring, the signs and symptoms of toxicity and what to do if they are experienced • Provide training for patient/carer and ensure they are familiar with how to administer somatropin

	• Be available to provide patient specific advice and support to GPs as necessary • Report any adverse events to the MHRA
15. Responsibilities of the GP	• Continuation GH therapy prescription, nine months after initiation of therapy. • Continue treatment once maintenance dose has been achieved by the specialist (i.e. after 9 months of treatment by specialist). • Notify the consultant team of any circumstances that may preclude the use of somatotropin, for example, the use of illicit drugs/excessive drinking or contraindications to treatment. • Ensure no drug interactions with concomitant medicines. • To monitor and prescribe in collaboration with the specialist according to this protocol. • Symptoms or results are appropriately actioned, recorded and communicated to secondary care when necessary. • GPs should reply to request for shared care to either accept or decline within 14 days. A form is available on the GMMMG website to facilitate this, if you so wish. • If the GP does not feel it is appropriate to take on the prescribing then the prescribing responsibilities will remain with the specialist. The GP should indicate the reason for declining. • Enter a READ code on to the patient record to highlight the existence of shared care for the patient. • Undertake more frequent monitoring tests at request of specialist if there is evidence of clinical deterioration, abnormal results, or symptoms suggesting abnormal hepatic function or other risk factors. Contact consultant team for advice on monitoring in these circumstances if required. • Monitor the patient's general wellbeing. • Seek urgent advice from secondary care if: ➢ Headache: If severe, recurrent, or associated with nausea and vomiting. ➢ The patient becomes pregnant ➢ Non compliance is suspected ➢ The GP feels a dose change is required ➢ The GP feels the patient is not benefiting from the treatment • The shared care agreement will cease to exist, and prescribing responsibility will return to secondary care, where: ➢ The clinical situation deteriorates such that the shared care criterion of stability is not achieved. ➢ The clinical situation requires a major change in therapy. ➢ GP feels it to be in the best stated clinical interest of the patient for prescribing responsibility to transfer back to the consultant team. The consultant team will accept such a transfer within a timeframe appropriate to the clinical circumstances. N.B. There must be discussion between the consultant team and GP on this matter and agreement from the consultant team to take back full prescribing responsibility for the treatment of the patient. The consultant team should be given 14 days' notice in which to take back prescribing responsibilities from primary care. • Report any suspected adverse drug reactions to the Specialist who initiated therapy under the shared care agreement, all adverse events should be reported even if causal relationship is not known or if the adverse event is already known about. • Report adverse events to the MHRA

<table>
<tr><td>16. Responsibilities of the patient</td><td colspan="4">Discuss potential benefits and side effects of treatment with the specialist and GP, to identify whether they have a clear picture of these from the specialist and to raise any outstanding queries.
Share any concerns they have in relation to treatment with their drug(s)
To take medication as directed by the prescriber, or to contact the GP if not taking medication
To attend hospital and GP clinic appointments
Failure to attend will result in medication being stopped (on specialist advice)
To report adverse effects to their Specialist or GP</td></tr>
<tr><td rowspan="2">17.Additional Responsibilities
e.g. Failure of patient to attend for monitoring, Intolerance of drugs, Monitoring parameters outside acceptable range, Treatment failure, Communication failure</td><td>List any special considerations</td><td>Action required</td><td>By whom</td><td>Date</td></tr>
<tr><td>[insert]</td><td>[insert]</td><td>[insert]</td><td>[insert]</td></tr>
<tr><td>18. Supporting documentation</td><td colspan="4">The SCG must be accompanied by a patient information leaflet. (available from www.medicines.org.uk).</td></tr>
<tr><td>20. Shared care agreement form</td><td colspan="4">Attached below</td></tr>
<tr><td>21. Contact details</td><td colspan="4">See Appendix 1</td></tr>
</table>

Appendix 1 – Local Contact Details

Lead author contact information	**Name:** *[insert text here]*
	Email: *[insert text here]*
	Contact number: *[insert text here]*
	Organisation: *[insert text here]*

Commissioner contact information	**Name:** *[insert text here]*
	Email: *[insert text here]*
	Contact number: *[insert text here]*
	Organisation: *[insert text here]*

Secondary care contact information	**If stopping medication or needing advice please contact:**
	Dr *[insert text here]*
	Contact number: *[insert text here]*
	Hospital: *[insert text here]*

Shared Care Guideline Summary:
GROWTH HORMONE IN ADULTS

Drug	Somatotropin (Growth Hormone)
Indication	Treatment of adults with growth hormone deficiency
Overview	Recombinant human growth hormone (Somatropin) treatment is recommended for the treatment of adults with severe growth hormone (GH) deficiency that is severely affecting their quality of life and they fulfill all three of the following NICE criteria (TA 64, August 2003): • They have severe growth hormone deficiency (GHD), 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. • They have an 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.
Specialist's Responsibilities	**Initial investigations:** Assess the patient & establish the need for Growth Hormone with provision of appropriate information on GHD and its treatment. Initiation of treatment and titration of dose based on IGF-1 levels including review of patient at monthly intervals for first three months. **Initial regimen:** Initial dose of 0.15 – 0.3 mg daily, gradually increased if required to maximum 1 mg daily; use minimum effective dose (requirements may decrease with age). 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 maintenance dose in these patients seldom exceeds 0.5 mg per day. **Clinical monitoring:** Clinical and laboratory supervision will take place in secondary care at 6-12 monthly intervals but on occasions, if an interim clinical or biochemical parameter monitoring (such as check of blood pressure; HBA1C; TFTs; Lipid Profile) is required, then patient's GP might be requested for the tests to be carried out in primary care by the Endocrinologist / Endocrinology team responsible for the patient. **Frequency:** 6-12 monthly intervals **Safety monitoring:** Monitoring for response and adverse drug reactions (ADRs) during initiation period. Evaluating ADRs raised by the GP and evaluating any concerns arising from reviews undertaken by GP. **Prescribing duration:** An initial 3-month period of somatropin dose titration, followed by a 6-month therapeutic trial period by the Consultant. Patients will only be transferred to GP after this. **Prescribing details:** Specialist initiated. Transferred to GP once stabilised. To stop the drug or provide GP with advice on when to stop this drug.

	Documentation: The consultant team will write formally to the GP to request shared care using the GMMMG agreed process. Patients will only be transferred to the GP once the GP has agreed. Provide GP with diagnosis, relevant clinical information, treatment plan, duration of treatment with 14 days of seeing the patient or inform GP if the patient does not attend appointment.
GP's Responsibilities	**Maintenance prescription:** Prescribe somatropin in accordance with the specialist's recommendations. Max dose 1mg per day. **Clinical monitoring:** To report to and seek advice from the specialist on any aspect of patient care which is of concern to the GP and may affect treatment. **Safety monitoring:** Monitoring for adverse drug reactions (ADRs) **Duration of treatment:** Stop treatment on advice of specialist. **Re-referral criteria:** Seek urgent advice from secondary care if: ➢ Headache: If severe, recurrent, or associated with nausea and vomiting. ➢ The patient becomes pregnant ➢ Non compliance is suspected ➢ The GP feels a dose change is required ➢ The GP feels the patient is not benefiting from the treatment ➢ Severe recurrent headache with nausea & vomiting. **Documentation:** GPs should reply to request for shared care to either accept or decline within 14 days. A form is available on the GMMMG website to facilitate this, if you so wish.
Adverse Events	See table below
Contra-indications Cautions Drug Interactions	Please refer to the BNF and/or SPC for information
Other Information	Treatment is self-administered by a daily subcutaneous injection. To avoid confusion, prescribers should specify the brand to be dispensed.
Contact Details	**Name:** *[insert text here]* **Address:** *[insert text here]* **Telephone:** *[insert text here]*

Adverse events	Action
Headache: If severe, recurrent, or associated with nausea and vomiting.	Report immediately to the GP / Specialist Endocrine Department. GH to be discontinued.
Signs of fluid retention: Such as peripheral oedema, stiffness in the extremities, arthralgia, myalgia and paraesthesia are common when starting somatropin	Usually mild to moderate and subsides spontaneously or with dose reduction. Discuss if persistent or severe paraesthesia present. Dose reduction by specialist may be necessary to avoid the development of carpal tunnel syndrome.
Lipoatrophy: May occur at site of injection	This can be avoided by varying the site of administration.
Insulin resistance: Diabetic patients on insulin may require increased insulin requirements	HbA1c should be monitored and patients advised accordingly by specialist
Hypothyroidism: Has been observed with somatropin	Thyroid function should be monitored by specialist