NHS Hertfordshire

Use of Somatostatin Analogues in Adult Patients with Acromegaly

Shared Care Guidelines

November 2011

Approved by Hertfordshire Medicines Management Committee
November 2011

This guidance has been adapted from the best available guidance, produced by the The Endocrine Society 2009 - The Journal of Clinical Endocrinology and Metabolism

No guidance was available from the following sources:

- **NICE guidance**
- **SIGN guidance**
- **Cochrane reviews**
- **National Library for Health**
- **National electronic Library for Medicines**
- **MeReC**
- **Bandolier**
- **BMJ Best Treatments**
- **Scottish Medicines Consortium**

Contents

Introduction

Acromegaly – the disease

Acromegaly is a relatively rare condition that affects approximately 2000 – 2500 people in Great Britain. The elevated growth hormone (GH) and insulin-like growth factor (IGF)-1 levels lead to a wide range of cardiovascular, respiratory, endocrine and metabolic morbidities. In recent studies there was a 32% increased risk for all-cause mortality in patients with acromegaly [(1)].

Cause	• Hypersecretion of GH by a pituitary tumour • Metabolic effects of elevated GH levels • Local and endocrine consequences of the pituitary tumour
Epidemiology **Incidence** **Prevalence**	• 4 to 5 new cases per million per year • 40 to 50 per million population
Clinical features & morbidity	• Coarse facial features (cosmetically disfiguring) • Enlargement of hands and feet • Soft tissue thickening (carpal tunnel syndrome) leading to paraesthesiae • Headache • Tiredness/lethargy • Excessive sweating • Prognathism, separation of teeth and macroglossia • Obstructive sleep apnoea • Cardiovascular disease (hypertension, cardiomyopathy) • Arthralgia (accelerated osteoarthritis) • Impaired glucose tolerance/diabetes mellitus • Goitre
All-cause increase in Mortality	• Cardiovascular disease (hypertension, heart disease, stroke) • Diabetes • Respiratory causes • Malignancy (colon and breast)

Treatment of acromegaly

The aims of treatment are to reduce or control tumour growth, inhibiting GH hypersecretion and normalising IGF-1 levels.

The disabling symptoms of the disease can be rapidly reversed by lowering GH and IGF-1 levels. Most of the features of acromegaly are also reversible, with the exception of established bone changes.

Several recent studies have demonstrated that the excess mortality observed in acromegaly can be reversed by lowering GH to values below 2.5ng/ml (<5mU/l) and/or normalising IGF-1 levels for age and sex [(1)].

Treatment options

There are three treatment options for patients with acromegaly:

Surgery	• Transsphenoidal surgery is the first – line therapy of choice for the majority of cases • In centres of excellence, surgery alone can produce a normalisation of IGF-1 in 75 - 95% of patients with intrasellar microadenomas [(1)]
Radiotherapy	• Indicated if surgery and or medical therapy is unsuccessful • Effective, but takes many years to exert its effect
Medical therapy	• Used to alleviate symptoms prior to surgery or radiotherapy • Some patients may require long-term medical therapy as an adjunct to surgery or radiotherapy • Some patients may be unsuitable for surgery (or radiotherapy) and may require primary medical therapy

Medical Therapy

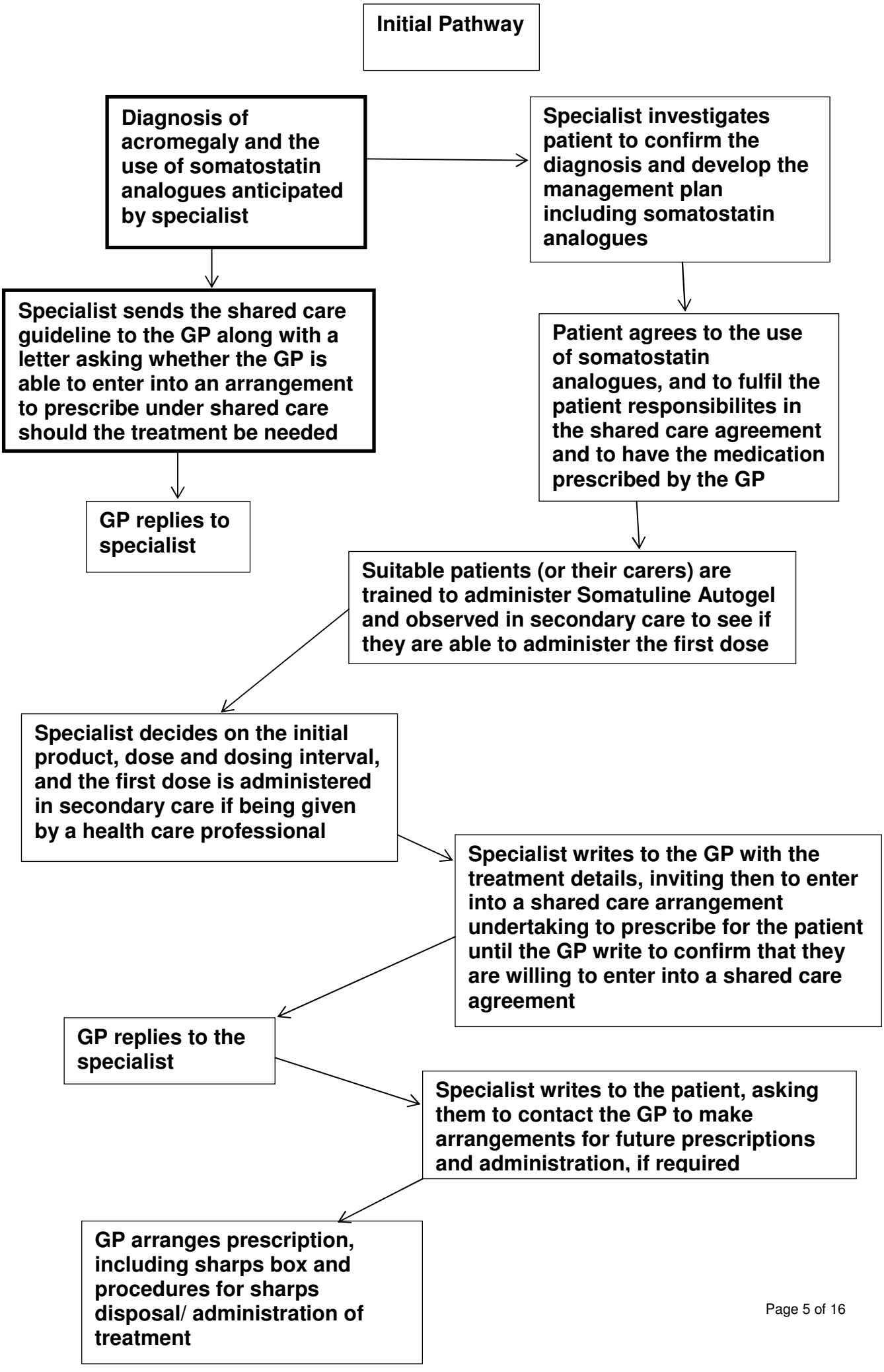
Currently, there are three drug classes available for the treatment of acromegaly: dopamine agonists (DAs), Somatostatin analogues, and a GH receptor antagonist (GHRA). For women who become pregnant while on medical therapy, cessation of medical therapy during pregnancy is usually advised, primarily based on the lack of a large database demonstrating the safety of such use. Please seek consultant endocrinologist's advice.

Somatostatin analogues, octreotide and lanreotide are first-line medical therapy. These synthetic analogues of the hypothalamic peptide, somatostatin, inhibit pituitary GH release and should suppress GH to <2.5ng/ml and normalise IGF-1 in up to 70% of cases [(1)]. Maximal benefit may be achieved after 10 years of therapy[(1)].

Prescribing of the somatostatin can be taken over by the GP under shared care arrangements once the patient has been able to tolerate the first dose, and once it is known whether they can self administer since this will affect the arrangements that the GP needs to make.

The specialist will review the patient and decide on dose adjustments which will be communicated by letter to the GP so that they can ensure that the correct dose is prescribed.

Since this document provides useful information about the condition, it should wherever possible be sent to the patient's GP as soon as the specialist has made the diagnosis and anticipates that the patient may need treatment with somatostatin analogues so that the GP has time to digest the contents and can reply to the specialist to indicate whether they are able to enter into shared care once a decision has been made about which treatment the patient is going to use.


Initial Pathway
Diagnosis of acromegaly and the use of somatostatin analogues anticipated by specialist
Specialist investigates patient to confirm the diagnosis and develop the management plan including somatostatin analogues
Specialist sends the shared care guideline to the GP along with a letter asking whether the GP is able to enter into an arrangement to prescribe under shared care should the treatment be needed
Patient agrees to the use of somatostatin analogues, and to fulfil the patient responsibilites in the shared care agreement and to have the medication prescribed by the GP
GP replies to specialist
Suitable patients (or their carers) are trained to administer Somatuline Autogel and observed in secondary care to see if they are able to administer the first dose
Specialist decides on the initial product, dose and dosing interval, and the first dose is administered in secondary care if being given by a health care professional
Specialist writes to the GP with the treatment details, inviting then to enter into a shared care arrangement undertaking to prescribe for the patient until the GP write to confirm that they are willing to enter into a shared care agreement
GP replies to the specialist
Specialist writes to the patient, asking them to contact the GP to make arrangements for future prescriptions and administration, if required
GP arranges prescription, including sharps box and procedures for sharps disposal/ administration of treatment

Responsibilities of Specialist Team, GP, and Patient in Shared Care Arrangement

Speciality Team Responsibility	GP Team Responsibility	Patient Responsibility
▪ Send the shared care agreement to the GP when the use of somatostatin analogues is anticipated so that the GP is informed about the condition and treatments and can consider whether they would be willing to enter into shared care if the medication is needed. ▪ Provide the patient with suitable written and verbal information about the drug prior to starting the medication and discuss the benefits and side effects of treatment. ▪ Carry out pre-treatment assessment of patient as set out in table on page 8 ▪ Advise women of child bearing age on the need for contraception. ▪ Train suitable patients or their carers to self administer the Somatuline Autogel® and on safe sharps disposal and assess whether they are able to successfully self administer. ▪ Be responsible for all routine monitoring whilst patient remains on the treatment (page 8) ▪ Discuss shared care with the patient and ensure that they are willing to undertake the patient responsibilities. ▪ Send this document and the Shared Care Agreement letter to the GP confirming that the patient is willing to fulfill the patient responsibilities, and asking the GP to confirm that they are willing to prescribe under shared care arrangements. ▪ Provide the GP with clear instructions as to what the product brand, dose, route and frequency interval is. ▪ Ensure that the patient receives supplies from the hospital until the GP formally agrees to share care. ▪ Communicate to the patient as to who will be prescribing the next dose. ▪ Specify review dates at clinically relevant time intervals and communicate this to patient and GP. ▪ Review the patient's condition and monitor response to treatment regularly ▪ Communicate any changes in treatment or dose requirements, results of monitoring undertaken and assessment of adverse events, to the GP. Adverse events must be reported to the CSM as well. ▪ Notify the GP if patient fails to attend for appropriate monitoring and advise GP on appropriate action. ▪ Advise the GP on when to stop treatment. ▪ Provide the GP with relevant contact information with clear arrangement for back-up advice and support should further assistance be required.	▪ GP to notify the consultant in writing, within two weeks of receiving the request, if they agree to share care for the patient. ▪ Take on prescribing from the second prescription ▪ Prescribe Sharps bins for patients who will be self-administering the Autogel® ▪ Make the necessary arrangements for the regular intramuscular administration of Sandostatin LAR or Somatuline LA ▪ Discuss contraception with women of child bearing age at each annual medication review. ▪ Contact the specialist if there is a change in the patient's health status. ▪ Report and seek advice from a specialist on any aspect of patient care which is of concern to the GP and may affect treatment. ▪ Report any adverse effects reported by the patient to the specialist and CSM. ▪ Stop treatment in the case of a severe adverse event and await advice from the Consultant	▪ Report any adverse effects of treatment to their Specialist team or GP ▪ Report to the Specialist team or GP if they do not have a clear understanding of their treatment ▪ Female patients should inform their GP and specialist if they are planning a pregnancy or become pregnant. ▪ Female patients between 15 and 50 should ensure they are using effective contraception for as long as they are on treatment ▪ Attend for monitoring as set out in the shared care guideline. ▪ Get their prescriptions dispensed by the same community pharmacy as the prescription may need to be ordered in advance.

Medical Therapy

	Preparation	Recommended administration
First line treatment	**Somatuline Autogel®** Lanreotide depot preparation	**60mg, 90mg or 120mg administered by deep subcutaneous into the superior, external quadrant of the buttock. Frequency: every 28 days*.** **Expectation is that the patient or their carer will self administer. If they are unable to do so, the reason for this should be included in the letter to the GP, along with the reason why they do not have someone who can administer the injection for them, since attending to have the injection administered by a health care professional increases the costs associated with the treatment [(6)].**
Alternative treatment	**Sandostatin LAR®** Octreotide depot preparation	**10mg, 20mg or 30 mg to be injected intramuscularly every 28 days by deep intragluteal injection. The site of repeat intragluteal injections should be alternated between the left and right gluteal muscle [(7)].** **Injection is for administration by a health care professional which increases the costs associated with the treatment.**
Alternative treatment	**Somatuline LA®** Lanreotide	**30mg administered every 7, 10 or 14 days by deep intramuscular injection into gluteal muscle [(5)].** **Injection is for administration by a health care professional which increases the costs associated with the treatment.**

*Frequency interval may be increased depending on patient response

This information needs to be read in conjunction with Appendix 1.

Assessments and Monitoring

Pre-treatment assessment by Specialist:

Insulin Growth Factor – 1
Growth Hormone levels
Colonoscopy
Ultrasound scanning of the gall bladder
Oral Glucose Tolerance Test

During treatment: See 'Responsibilities of Speciality Team, GP, and Patient in Shared Care Arrangement'

Investigation	Frequency	Specialist	GP
Insulin Growth Factor – 1	One to three monthly for 6 months then on annual review or earlier depending on clinical need	✓	
Growth Hormone levels	One to three monthly for 6 months then on annual review or earlier depending on clinical need	✓	
Blood glucose monitoring in diabetic patients	As usual for diabetic patients		✓
HbA1c in diabetic patients	Annual or more frequently if control is poor		✓
Thyroid Function	Annual	✓	
FBC and LFT's	Depending on clinical need	✓	
Vitamin B_{12} Levels (in patients with a history of B_{12} deprivation)	Annual or depending on clinical lead	✓	
Prolactin	Depending on clinical need	✓	
Oral Glucose Tolerance Test	Annual if baseline results abnormal	✓	
U&E and Creatinine	Depending on clinical need	✓	
Cortisol	Depending on clinical need	✓	
***Ultrasound scanning of the gall bladder**	6 monthly depending on clinical decision	✓	

*See special recommendations on the next page

Special recommendations

- Development of gallstones has been reported in 10-20% of patients receiving octreotide or lanreotide. Ultrasound examination of the gallbladder before and at about 6 monthly intervals during treatment is recommended in the SPC but many consultants do not consider that ultrasound monitoring during treatment is necessary. The referring consultant should inform the GP in writing of their clinical decision regarding gallbladder disease monitoring.
- Diabetic patients should be monitored for the need for changes to anti-diabetic therapy.

Contraindications

- Hypersensitivity to lanreotide or octreotide, lactide-glycolidecopolymer, lactic-glycolic copolymer, mannitol, carmellose or polysorbate 80.
- Experience with lanreotide or octreotide in pregnancy or breastfeeding is not available and thus not recommended.

Cost

- These drugs are excluded from the PbR tariff (for hospital use) so the costs are passed on to the commissioners whether they are prescribed in primary or secondary care.
- Costs at September 2013 are (current costs are available in the BNF (www.bnf.org) and eMC Dictionary of Medicines and Devices Browser (http://dmd.medicines.org.uk/DesktopDefault.aspx):

Somatuline Autogel®

60mg	£551
90mg	£736
120mg	£937
Annual cost range:	£7,163 - £12,181

plus cost of up to 13 injection appointments for patients who are unable to self-administer

Sandostatin® LAR®

10mg	£470
20mg	£776
30mg	£993
Annual cost range:	£6,108 - £12,915

plus cost of up to 13 injection appointments

Somatuline LA®

30mg	£323
Annual cost range:	£8,398 - £16,796

plus cost of 13 to 52 injection appointments

Side Effects

Very Common > (1 in 10) > Common > (1 in 100) > Uncommon > (1 in 1000) > Rare > (1 in 10000) > Very rare

Very common/common

- Injection site reactions (local pain and rarely, swelling and rash)
- Gastrointestinal side effects (diarrhoea, nausea, cramping, abdominal discomfort) in 50% of patients initially, with persistent symptoms in 10% of patients.
- Other gastrointestinal side effects include anorexia, flatulence and steatorrhoea. Biliary tract abnormalities in 50% of patients (due to reduced gall bladder motility), with new gall stones in 10-20% of long-term patients, which are usually asymptomatic.
- Abnormalities of glucose metabolism (hyperglycaemia in 7-15% of patients due to reduced insulin secretion, hypoglycaemia in 2% of patients).
- Hypothyroidism (2% of patients).
- Bradycardia
- Pruritis, rash, alopecia
- Elevated transaminase levels, hyperbilirubinaemia

Uncommon/Rare

- Symptoms resembling acute intestinal obstruction
- Depressed B_{12} levels
- Acute pancreatitis has been reported within the first hours or days
- Cholelithiasis-induced pancreatitis
- Acute hepatitis without cholestasis
- Tachycardia
- Dehydration

Common/ Significant Drug interactions

- **Antidiabetic medication**: May require change in anti-diabetic medicine doses: (metformin, sulphonylureas, 'glitazones', 'glinides' and insulin) as somatostatin analogues can alter drug requirements due to inhibitory effects on the secretion of insulin and glucagons.
- **Ciclosporin**: Possible reduced intestinal absorption of ciclosporin leading to lower plasma levels
- **Cimetidine**: Possible delayed absorption of cimetidine
- **Bromocriptine**: Possible increase in the bioavailability of bromocriptine.
- Drugs metabolised by **cytochrome P450** May decrease metabolic clearance of compounds metabolised by cytochrome P450 enzymes. Caution should be exercised during co-administration of octreotide and drugs mainly metabolised by CYP3A4, which have a narrow therapeutic index (e.g. carbamazepine, digoxin, warfarin and terfenadine).
- **Bradycardia –inducing drugs** (e.g. beta blockers) – concomitant administration of bradycardia –inducing drugs may have an additive effect on the slight reduction of heart-rate associated with somatostatin analogues. Dose adjustments of such concomitant medications may be necessary.

Contact information

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References

1. The Journal of Clinical Endocrinology and Metabolism. The Endocrine Society 2009 94:1509-1517. Guidelines for Acromegaly Management: An Update

2. NHS Lincolnshire Shared Care Guideline, September 2010. Octreotide for the treatment of acromegaly

3. North and East Devon Healthcare Community Shared Care Prescribing Guideline, March 2008. Treatment of acromegaly in adults. Somatostatin analogues

4. Society for Endocrinology, September 2006. The use of somatostatin analogues and the GH receptor antagonist in patients with acromegaly.

5. Summary of Product Characteristics, Ipsen Ltd, September 2003, updated on eMC 19/10/10. Somatuline LA

6. Summary of Product Characteristics, Ipsen Ltd, April 2008. Somatuline Autogel 60mg, Somatuline Autogel 90 mg, Somatuline Autogel 120mg

7. Summary of Product Characteristics, Novartis Pharmaceuticals UK Ltd, November 2007, updated on eMC 02/03/11. Sandostatin LAR

This guidance does not replace the SPC, which should be read in conjunction with the guidance.

Appendix 1

Somatuline Autogel®

Dosage and Administration [6]

In patients receiving a somatostatin analogue for the first time, the recommended starting dose is 60mg of Somatuline Autogel® administered every 28 days.

In patients previously treated with Somatuline LA® 30mg once every 14 days, the initial dose of SOMATULINE AUTOGEL® should be 60mg every 28 days; in patients previously treated with Somatuline LA® 30mg once every 10 days, the initial dose of SOMATULINE AUTOGEL® should be 90mg every 28 days; and in patients treated with Somatuline® LA 30mg once every 7 days, the initial dose of SOMATULINE AUTOGEL® should be 120mg every 28 days. Thereafter, for all patients, the dose should be individualised according to the response of the patient (as judged by a reduction in symptoms and/or a reduction in GH and/or IGF-1 levels).

For patients whose GH concentration are below 1ng/mL (approx 2mU/L), whose IGF-1 serum concentrations have normalised, and in whom most reversible signs of acromegaly have disappeared, the monthly dose should be decreased. If appropriate, this may be achieved by giving Somatuline Autogel® 120mg at increased intervals of 42-56 days.

For patients on Somatuline Autogel® 60mg or 90mg every 28 days who are well controlled (GH concentrations less than 2.5ng/mL (approx 5mU/L) but above 1ng/mL (approx 2mU/L) and normalised IGF-1 levels) the dose should be maintained, or alternatively Somatuline Autogel® 120mg may be given at increased intervals of 56 or 42 days respectively.

For patients in whom clinical symptoms and biochemical parameters are not adequately controlled (GH concentrations still above 2.5ng/mL (approx 5mU/L) or IGF-1 greater than age matched normal) the dose of Somatuline Autogel® may be increased to a maximum of 120mg at 28 day intervals.

Method of administration

SOMATULINE AUTOGEL® should be injected, via the deep subcutaneous route, into the superior, external quadrant of the buttock.
The injection may be given by a healthcare professional, or, for patients considered by their healthcare professional to be stabilised on their treatment with Somatuline Autogel®, by an appropriately trained friend or relative of the patient. Alternately, such patients may self-administer the product after appropriate training. In this case the injection should be given in the upper, outer thigh.
Regardless of the site of administration, the skin should be stretched prior to injection. The needle should be inserted rapidly to its full length, perpendicularly to the skin. The injection site should be alternated between the right and left sides.

Dosage and Administration [7]

For patients who have not received prior treatment with subcutaneous Sandostatin, a test dose of s.c. octreotide (50-100mcg) is recommended to assess any adverse reaction to octreotide prior to initiating treatment with Sandostatin LAR®. Treatment with Sandostatin LAR® can be started on the day after the last dose of S.C. octreotide.

For de novo patients who have received a test dose and for patients who are adequately controlled with S.C. octreotide, treatment should be started with 20mg Sandostatin LAR® intramuscularly at 4-week intervals for 3 months. Subsequent dosage adjustment should be based on serum GH and IGF 1/somatomedin C concentrations and clinical symptoms.

For patients in whom clinical symptoms and biochemical parameters (GH; IGF 1) are not fully controlled (GH concentrations still above 2.5µg/L{5mU/L}), the dose may be increased to 30mg every 4 weeks.

For patients whose GH concentrations are consistently below 1µg/L (2mU/L), whose IGF 1 serum concentrations have normalised, and in whom most reversible signs/symptoms of acromegaly have disappeared after 3 months of treatment with 20mg, the dose may be reduced to 10mg every 4 weeks. However, in this group of patients' serum GH and IGF 1 concentrations and clinical signs/symptoms should be monitored particularly closely.

For patients on a stable dose of Sandostatin LAR®, assessment of GH and IGF should be made every 12 months. Six-monthly monitoring may be necessary in those patients whose clinical and biochemical control is less adequate.
In order to permit successful endocrine testing of the completeness of tumour removal 5-6 weeks post surgery, the last injection of Sandostatin LAR® should be administered at least 3-4 weeks prior to surgery.

Instructions for i.m. injection of Sandostatin LAR® for deep intragluteal injection only

Remove the cap from vial containing Sandostatin LAR®. Assure that the powder is settled at the bottom of the vial by lightly tapping the vial. Remove the cap from the vehicle syringe. Attach one of the supplied needles to the vehicle syringe.

Insert needle through centre of rubber stopper of the Sandostatin LAR® vial. Without disturbing the Sandostatin LAR® powder, gently inject the vehicle into the vial by running the vehicle down the inside wall of the vial. Do not inject the vehicle directly into the powder. Withdraw any excess air present in the vial.

Do not disturb the vial until the vehicle has wetted the Sandostatin LAR® powder for suspension. Once complete wetting (approximately 2-5 minutes) has occurred, the vial should be moderately swirled until a uniform suspension is achieved. Do not vigorously shake the vial.

Immediately draw 2ml of air into the syringe and re-insert the needle through the rubber stopper. Inject the 2ml of air into the vial and then, with the bevel down and the vial tipped at approximately 45 degree angle, slowly draw the entire contents of the vial containing the suspension into the syringe. Immediately change the needle (supplied).

Gently invert the syringe as needed to maintain a uniform suspension. Eliminate air from syringe and disinfect the injection site. Insert needle into right or left gluteus and draw back to ensure that no blood vessel has been penetrated. Immediately inject i.m. by deep intragluteal injection.

Sandostatin LAR® must be given only by intragluteal injection, never i.v. If a blood vessel has been penetrated, select another injection site.

Somatuline LA® 30mg

Dosage and Administration [5]

Initially, one intramuscular injection should be given every 14 days. The frequency of subsequent injections may be varied in accordance with the individual patient's response (as judged by a reduction in symptoms and/or a reduction in GH and/or IGF-1 levels) such that injections can be given every 7 to 10 days as necessary.

NB: When converting over from Somatuline® to Sandostatin LAR® in out-patient clinics or on wards, contact the consultant endocrinologist for advice.

For further and most recent information, including information on interactions, adverse effects and dosing in patients with renal/hepatic impairment, always consult the latest version of the Summary of Product Characteristics (SPC), which can be found at: http://www.medicines.org.uk/

Shared Care Agreement Letter – Consultant Request – where treatment has started

To: Dr …….

Practice Address: ……...

……..

Patient Name:
NNN: **Date of Birth:**
Address:

DIAGNOSED CONDITION:

……..

I recommend treatment with the following drug: (Specify product by brand name, dose, dosing interval & route)

……..

The patient's next dose is due on……

The patient or their carer are able to administer the treatment*/ the treatment will need to be administered by a health care professional*

I am requesting your agreement to sharing the care of this patient according to the West Herts and East and North Herts NHS Trust and Hertfordshire PCT Shared Care Prescribing Guidelines for this drug. I enclose a copy of the shared care guidelines.

Signed	
Consultant name	
Department	
Contact number	
Date	

GP RESPONSE

I agree / do not agree* to share the care of this patient in accordance with the Shared Care Guideline and am able to do so from…….(insert date)

Signed: ……. Date: ……

GP name: ……. *Delete as appropriate

Shared Care Agreement Letter – Consultant Request – where treatment has not yet started

To: Dr …….

Practice Address: ……...

……..

……..

Patient Name:
NNN:
Date of Birth:
Address:

DIAGNOSED/SUSPECTED CONDITION:

……..

I anticipate that the patient will need treatment with somtatostatin analogues. I enclose a copy of the agreed shared care guidelines and am writing to ask whether you agree to prescribe under shared care arrangements should the patient need to start on the treatment.

Signed	
Consultant name	
Department	
Contact number	
Date	

GP RESPONSE

I would* / would not* be willing to share the care of this patient in accordance with the Shared Care Guideline if they need to start on somatostatin analogue treatment

Signed: ……. Date: ……

GP name: ……. *Delete as appropriate