New Medicine Recommendation

Octreotide (Sandostatin, Sandostatin LAR®) and Lanreotide (Somatuline Autogel, Somatuline LA®) Unlicensed use for orthostatic intolerance disorders e.g. postural orthostatic tachycardia syndrome (PoTS)

Recommendation: Black

NOT recommended for use by the NHS in Lancashire.

There is insufficient evidence of the effectiveness of octreotide and lanreotide in orthostatic intolerance disorders.

Summary of supporting evidence:

- The safety profile of octreotide and lanreotide is well established and published studies relating to the proposed used have not raised any additional safety concerns.
- One study assessed octreotide use in combination with midodrine versus midodrine which may reflect a suitable place in the treatment pathway for octreotide.
- Octreotide/lanreotide provides an additional treatment option for patients with refractory orthostatic intolerance who have not fully responded to other non-pharmacological and pharmacological treatments.
- If two patients were treated with the highest dose of long-acting octreotide (most expensive permutation) the annual acquisition cost would be as follows:
  2 X £11,244= **£22,488**
  If one patient was treated with the lowest dose octreotide (least expensive permutation) the annual acquisition cost would be as follows:
  1 X £2,171 = **£2,171**
- There is a lack of additional safety and quality of life data in the studies relevant to the proposed uses.

Details of Review

Name of medicine (generic & brand name)**:**

Octreotide (Sandostatin, Sandostatin LAR®) and Lanreotide (Somatuline Autogel, Somatuline LA®). [1] [2]

Strength(s) and form(s):

Octreotide:

- 50 mcg/ml, 100 mcg/ml, 200 mcg/ml and 500 mcg/ml solution for injection and infusion;
- long acting preparations: 10 mg, 20 mg and 30 mg powder and solvent for suspension for injection. [1]

Lanreotide:

- Long acting preparations: 60 mg, 90 mg and 120 mg solution for injection in a prefilled syringe; 30 mg powder for suspension for injection. [2]

Dose and administration:

Unlicensed use, dose based on those used across observational studies:

Octreotide long acting 10 mg monthly

Octreotide 50–100 mcg two or three times daily

No doses available in the literature for lanreotide in this indication

BNF therapeutic class / mode of action:

Pituitary and hypothalamic hormones and analogues / somatostain analogues which have a range of actions on various endocrine, neuroendocrine, exocrine and paracrine functions. [3]

Licensed indication(s):

Octreotide - acromegaly, gastro-entero pancreatic endocrine tumours, complications following pancreatic surgery, bleeding gastro-oesophageal varices, treatment of TSH-secreting pituitary adenomas. [1]

Lanreotide – acromegaly, treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease, treatment of symptoms associated with neuroendocrine tumours, thyrotropic adenomas. [2]

Please note that licensed indications vary between different formulations of octreotide and lanreotide. Please consult product SPCs for further information.

Proposed use (if different from, or in addition to, licensed indication above):

Unlicensed use in gastrointestinal bleeding disorders (including small bowel dysplasia, gastric antral vascular ectasia, haemorrhagic telangiectasia).

Course and cost:

Octreotide long acting (Sandostatin LAR®): 10 mg monthly

Annual cost (12 injections): £6,596.52

Octreotide (Sandostatin®): 50-100 mcg two to three times daily

Annual cost £2,171.02 to £6,125.43

Current standard of care/comparator therapies for orthostatic hypotension:

- Non-pharmacological management options are recommended first-line (including compression stockings, blood pressure monitoring and increased water and salt ingestion).
- Pharmacological treatment with off-label fludrocortisone or midodrine alone or in combination. [4]

N.B. Other unlicensed treatments with limited evidence base include selective serotonin reuptake inhibitors, pyridostigmine and erythropoietin.

Relevant NICE guidance:

NICE Evidence Summary [ESNM61]: Orthostatic hypotension due to autonomic dysfunction: midodrine. [4]

Background and context

Postural orthostatic tachycardia syndrome (PoTS) is an abnormal response of the autonomic nervous system and is characterised by orthostatic intolerance. Orthostatic (or postural) hypotension results from an inadequate physiological response to postural changes in blood pressure. In people with the condition, standing leads to an abnormally large drop in blood pressure, which can result in symptoms such as light-headedness, dizziness, blurring of vision, syncope and falls. [4] It may be the initial sign of autonomic failure and cause major symptoms in many primary and secondary diseases of the autonomic nervous system (ANS) (e.g. pure autonomic failure (PAF), multiple system atrophy (MSA), Parkinson's disease).

The Individual Funding Requests team at Midlands and Lancashire Commissioning Support Unit have received requests for the use of octreotide in the management of PoTS. Consequently, the Lancashire and South Cumbria Medicines Management Group agreed to prioritise octreotide/lanreotide treatment for a New Medicines Review.

Summary of evidence

Summary of efficacy data in proposed use:

There are no randomised controlled clinical trials assessing the efficacy and safety of octreotide or lanreotide for the treatment of PoTS or associated disorders causing orthostatic hypotension. The observation studies available only report outcomes in a very small number of patients (<70 patients in total) with many of the studies relating to other conditions resulting in postural hypotension e.g. multiple system atrophy (MSA), autonomic neuropathy.

K Kanjwal et al [5]

The study was a retrospective patient record analysis of 12 patients diagnosed with orthostatic intolerance who had failed multiple medications and were ultimately tried with octreotide. Patients underwent tilt-table testing which consisted of a 70° baseline upright tilt for a period of 30 minutes, during which time heart rate and blood pressure were monitored continually. If symptomatic hypotension and bradycardia occurred, reproducing a patient's symptoms, the test was ended. If no symptoms occurred, the patient was lowered to the supine position and an intravenous infusion of isoprenaline (a non-selective β adrenoreceptor agonist) started with a dose sufficient to raise the heart rate to 20% to 25% above the resting value. Upright tilt was then repeated for a period of 15 minutes. Octreotide was administered by subcutaneous injection beginning at 50 mg two to three times daily and titrating to the maximum dose of 100 mg three times daily.

Information was collected about the symptoms of orthostatic intolerance and before and 2 months after initiating octreotide. Symptoms of syncope and orthostatic palpitations improved in six (50%) of the patients. Three patients (25%) reported complete elimination of syncope, whereas another three had reduction in the frequency and severity of their syncope. However, symptoms of fatigue experienced by seven patients improved only in two. The remaining five patients continued to have debilitating fatigue when subsequently treated with modafinil. Also, six (50%) patients reported subjective improvement in their activities of daily living and were able to resume their employment or colleges.

R Hoeldtke et al (2007) [6]

Patients with autonomic neuropathy and chronic orthostatic hypotension were eligible for this two protocol study. Two of the participants had Parkinson's Disease and were disabled from orthostatic hypotension, two patients had pure autonomic failure and seven patients had orthostatic intolerance.

Protocol 1: Four patients with autonomic neuropathy were initiated on 7 mg of octreotide LAR before titrating upwards to a maximum of 30 mg based on evaluation of orthostatic response All four patients with autonomic neuropathy showed a pressor response to octreotide LAR and three

had a definite improvement in symptoms. Sensitivity to the pressor effect varied considerably. A dramatic clinical benefit was observed in one patient whose recurrent postprandial syncope (approximately 50 episodes/month) responded to low doses (7–15 mg) of the drug. The remaining three patients showed response to octreotide in terms of standing time, heart rate and blood pressure although an excessive potentially dangerous response to 30 mg persisted for a month in one patient.

Protocol 2: Seven patients with orthostatic intolerance were initiated on 10 mg of octreotide LAR before being titrated up to 30mg after 9 weeks of treatment, five completed the study. Octreotide LAR improved orthostatic tolerance in six of seven patients. Two patients, however, withdrew from the study. For the remaining five patients the most benefit was observed, 2 weeks after the 30 mg dose at which time the standing time was improved (55.5 ± 5 minutes vs. 36.0 ± 9 minutes pre-treatment, P < .01). Two patients were treated chronically with octreotide LAR. One patient was administered octreotide every 4–6 weeks for the last 5 years of his life. Therapy continued to suppress his post-prandial syncope and orthostatic syncope. Another patient had orthostatic syncope, chronic fatigue and headaches and was treated chronically with octreotide LAR for 3 years. The therapeutic effect has persisted during chronic therapy.

R Hoeldtke et al (1998) [7]

Twelve patients with autonomic neuropathy and chronic orthostatic hypotension participated in this study comparing midodrine and octreotide to each other and in combination. Patients selected for this protocol had, on previous days, received octreotide (0.3– 0.5 mg/kg). After an overnight fast, patients were instructed to rest with the head of the bed elevated 30° for at least 15 minutes (before measuring standing times) and then, on separate days, they received (according to a randomised design) either midodrine (10 mg, orally), octreotide (1.0 mg/kg, sc), or no treatment. Nine of the 12 participants in this protocol, after receiving each drug individually, agreed to be treated with the combination of midodrine and octreotide.

In the absence of treatment, the patients with autonomic neuropathy were able to stand 3.5 ± 0.7 min. After midodrine, standing time was 8.4 ± 2.7 min (P = 0.11); after octreotide, standing time increased to 13.2 ± 3.9 min (P = 0.0034). The subset of patients (n = 9), treated with both midodrine and octreotide, stood for 21.2 ± 5.5 min (difference from no treatment, P = 0.0002). Combination therapy was more effective than midodrine only (P = 0.002) and octreotide only (P = 0.036).

M Alam et al [8]

Eighteen subjects with primary autonomic failure were studied in a randomised manner on two occasions with and without octreotide (1 mcg/kg BD). All subjects were on 100 mcg of fludrocortisone each night which was continued throughout the study. Measurements of 24-hour blood pressure and heart rate were made, and symptoms were monitored. There was a reduction in:

- postural (supine versus standing: from 96/62mmHg without treatment to 106/67mmHg with treatment),
- postprandial (107/65mmHg to 122/75mmHg) and
- exertion-induced (96/61mmHg to 113/71mmHg) hypotension.

The authors concluded that after octreotide patients were symptomatically better postprandially and subjects were able to walk with fewer symptoms following octreotide administration.

R Bordet et al [9]

The aim of this study was to determine the potential effect of octreotide chronic administration on the functional prognosis of patients suffering from multiple system atrophy. Five patients who had previously tried antihypotensive agents were studied although 2 patients were unable to participate in the acute phase of the study. The effects of octreotide (100 mcg sc injections TDS) were evaluated before and after 6 months of treatment through self-reported frequency and severity of dizziness and syncope. In the acute phase of the study, the three patients were

placed on a tilt table to assess their tolerance to a 60° head-tilt. Octreotide administration produced an improvement in tilt test tolerance. In the 6 month phase of the trial, using self-assessment charts, all five patients demonstrated a reduction in both severity and frequency of dizziness and syncope. Mean rating of the Barthel Scale,[a] used to measure performance in activities of daily living, increased from 21 to 37 after 6 months of treatment.

Other efficacy data:

N/A

Summary of safety data:

Safety data from studies relating to cohorts of patients with PoTS is limited although the predominant complication of therapeutically raising blood pressure while sitting is supine hypertension. The doses of the somatostatin analogues octreotide/lanreotide used in the above studies for the proposed use are within the bounds of the licensed doses stated in the Summary of Product Characteristics (SPCs) for each agent. Lanreotide and octreotide are therefore anticipated to have a similar safety profile in the proposed use to that demonstrated in the licensing studies of the products. The adverse effects listed in the SPC for lanreotide are summarised below and align with the adverse events listed for octreotide:

System organ class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Post-marketing safety experience (frequency not known)**
Infections and infestations				Injection site abscess
Metabolism and nutrition disorders		Hypoglycaemia, decreased appetite, hyperglycaemia, diabetes mellitus		
Psychiatric disorders			Insomnia	
Nervous system disorders		Dizziness, headache, lethargy		
Cardiac disorders		Sinus bradycardia		
Vascular disorders			Hot flushes	
Gastrointestinal disorders	Diarrhoea, loose stools, abdominal pain	Nausea, vomiting, constipation, flatulence, abdominal distension, abdominal discomfort, dyspepsia, steatorrhoea	Faeces discoloured	Pancreatitis
Hepatobiliary disorders	Cholelithiasis	Biliary dilatation		Cholecystitis
Musculoskeletal and connective tissue disorders		Musculoskeletal pain, myalgia		
Skin and subcutaneous tissue disorders		Alopecia, hypotrichosis		

[a] The Barthel Scale measures performance in activities of daily living (ADL), measuring the degree of assistance required by an individual on 10 items of mobility and self care ADL. Scores of 0-20 indicate "total" dependency, 21-60 indicate "severe" dependency, 61-90 indicate "moderate" dependency, and 91-99 indicates "slight" dependency.

General disorders and administration site conditions		Asthenia, fatigue, injection site reactions (pain, mass, induration, nodule, pruritus)		
Investigations		ALAT increased, ASAT abnormal, ALAT abnormal, blood bilirubin increased, blood glucose increased, glycosylated haemoglobin increased, weight decreased, pancreatic enzymes decreased	ASAT increased, blood alkaline phosphatase increased, blood bilirubin abnormal, blood sodium decreased*	
Immune system disorders				Allergic reactions (including angioedema, anaphylaxis, hypersensitivity)

Special warnings for the use of the somatostatin analogues include:

- The need to periodically monitor for gallstone formation;
- The risk of hypoglycaemia and hyperglycaemia and need to monitor blood glucose at treatment initiation;
- The slight risk of decreased thyroid function and need for thyroid function test at treatment initiation;
- The risk of bradycardia especially in patients with underlying cardiac problems.

Strengths and limitations of the evidence:

Strengths

- The safety profile of octreotide and lanreotide is well established and published studies relating to the proposed used have not raised any additional safety concerns.
- One study assessed octreotide use in combination with midodrine versus midodrine which may reflect a suitable place in the treatment pathway for octreotide.
- Octreotide provide an additional treatment option for patients with refractory orthostatic intolerance who have not fully responded to other non-pharmacological and pharmacological treatments.

Limitations

- There is a lack of robust randomised controlled clinical trials data to support the use of somatostatin analogues in the proposed indications.
- The outcomes data published in the observation studies has either not undergone robust statistical analysis or has very wide confidence intervals.
- There are no available studies relating to lanreotide use in PoTS and other types of orthostatic intolerance.
- There is a lack of additional safety data and quality of life data in the studies relevant to the proposed uses.
- There are no studies investigating lanreotide use in the proposed indication.

Summary of evidence on cost effectiveness:

N/A

Prescribing and risk management issues:

Octreotide and lanreotide are administered by subcutaneous injection. Patients may be trained to self-administer following initiation by a professional who is trained in the subcutaneous administration of medicines.

The BNF states that patients initiated on lanreotide should be monitored for hypothyroidism when clinically indicated. For octreotide the BNF advises to monitor thyroid function and liver function. [3]

The SPCs for both lanreotide and octreotide recommend monitoring for the development of gall stones. Monitoring of blood glucose and bradycardia may also be indicated in patients depending on their clinical history and risk of developing hypoglycaemia/hyperglycaemia and bradycardia

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per year (ex VAT)
Octreotide (Sandostatin®)	50-150 mcg two to three times daily	£14.87 for 5 x 50mcg amps	£2,171.02 to £6,125.43
Octreotide long-acting (Sandostatin LAR®)	10 mg per month	30mg = £549.71	£6,596.52
Lanreotide (Somatuline Autogel®)	120mg per month (NB estimated dose equivalent to the dose used for other indications as no studies have investigated use in proposed indication)	120mg = £937.00	£11,244
Costs based on Electronic Drug Tariff list prices November 2019 This table does not imply therapeutic equivalence of drugs or doses.			

Innovation, need and equity implications of the intervention:

Postural Tachycardia Syndrome (PoTS) can be a life altering and debilitating health condition. Simply standing up can be a challenge for affected people as their body is unable to adjust to gravity. [10] For patients with refractory PoTS who are not adequately managed using non-pharmacological measures and other pharmacological options, octreotide/lanreotide provide an alternative treatment option.

Financial implications of the intervention:

Based on a data provided by the Individual Funding Requests team, seven requests were made for the supply of either octreotide or lanreotide for the management of PoTS (or other orthostatic intolerance disorders) across Lancashire and South Cumbria between January 2017 and August 2019. This equates to one or two patients per year across Lancashire and South Cumbria.

If two patients were treated with the highest dose of long-acting octreotide (most expensive permutation) the annual acquisition cost would be as follows:

2 X £11,244= **£22,488** If one patient was treated with the lowest dose octreotide (least expensive permutation) the annual acquisition cost would be as follows: 1 X £2,171.02 = **£2,171.02** Please note that the data from the Individual Funding Requests team only outlines treatments that have been billed to the CCGs. Actual usage may be higher. It is also important to consider that if patients were not treated with octreotide/lanreotide, they may be treated with an alternative intervention e.g. another off-label pharmacological treatment. The overall additional cost of using lanreotide/octreotide is therefore likely to be significantly lower than the numbers stated above.
Service Impact Issues Identified:
Although the use of octreotide/ lanreotide for orthostatic intolerance e.g. PoTS would require additional monitoring it is not anticipated that their use would impact capacity in the system due to the small patient numbers. It would be expected that this cohort of patients would already be under the supervision of a specialist.
Equality and Inclusion Issues Identified:
None-identified.
Cross Border Issues Identified:
Both Pan Mersey APC and Greater Manchester Medicines Management Group do not currently have a position on the use of octreotide/lanreotide in the management of PoTS. The position agreed across Lancashire and South Cumbria should therefore not create any cross-border issues.
Legal Issues Identified:
N/A
Media/ Public Interest:
N/A

References

[1] Electronic Medicines Compendium, "Summary of Product Characteristics Sandostatin LAR 20mg," Novartis Pharmaceuticals UK Ltd, March 2018. [Online]. Available: https://www.medicines.org.uk/emc/product/1038/smpc. [Accessed 18 October 2019].

[2] Electronic Medicines Compendium, "Summary of Product Characteristics Somatuline Autogel 60mg," Ipsen Ltd, 16 October 2018. [Online]. Available: https://www.medicines.org.uk/emc/product/4808/smpc. [Accessed 18 October 2019].

[3] Joint Formulary Committee, "British National Formulary (online)," London BMJ Group and Pharmaceutical Press, [Online]. Available: http://www.medicinescomplete.com. [Accessed October 2018].

[4] National Institute for Health and Care Excellence, "Orthostatic hypotension due to autonomic dysfunction: midodrine evidence summary," 6 October 2015. [Online]. Available: https://www.nice.org.uk/advice/esnm61/chapter/Key-points-from-the-evidence. [Accessed 29 November 2019].

[5] K Kanjwal et al, "Use of Octreotide in the Treatment of Refractory Orthostatic Intolerance," *American Journal of Therapeutics,* vol. 19, no. 1, pp. 7-10, 2010.

[6] R Hoeldtke et al, "Treatment of autonomic neuropathy, postural tachycardia and orthostatic syncope with octrotide LAR," *Clinical Autonomic Research,* vol. 17, pp. 334-340, 2007.

[7] R Hoeldtke et al, "Treatment of Orthostatic Hypotension with Midodrine and Octreotide," *Journal of Clinical Endocrinology and Metabolism,* vol. 83, no. 2, pp. 339-343, 1998.

[8] M Alam et al, "Effects of the peptide release inhibitor, octreotide, on daytime hypotension and on nocturnal hypertension in primary autonomic failure," *Journal of Hypertension,* vol. 13, pp. 1664-1669, 1995.

[9] R Border et al, "Octreotide in the Management of Orthostatic Hypotension in Multiple System Atrophy: Pilot Trial of Chronic Administration," *Clinical Neuropharmacology,* vol. 17, no. 4, pp. 380-383, 1994.

[10] POTS UK, "Home Page," PoTS UK, [Online]. Available: https://www.potsuk.org/. [Accessed 5 December 2019].

[11] NICE, "Evidence summary [ESNM61] Orthostatic hypotension due to autonomic dysfunction: midodrine," NICE, October 2015. [Online]. Available: https://www.nice.org.uk/advice/esnm61/chapter/Key-points-from-the-evidence. [Accessed 18 December 2019].

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality