

New Medicine Recommendation

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

Unlicensed use in secretory gastrointestinal disorders (e.g. enterocutaneous fistula, high output stoma and refractory diarrhoea)

Recommendation: Red

Octreotide and lanreotide are recommended for the treatment of secretory gastrointestinal disorders (e.g. enterocutaneous fistula, high output stoma and refractory diarrhoea). Initiation and continued supply of octreotide/lanreotide is the responsibility of hospital or specialist services.

Octreotide and lanreotide are not licensed for this indication and there is not a large body of evidence to support this unlicensed use.

Patients should be reviewed within 4 weeks of initiation of somatostatin analogues. Continuation of treatment should only be recommended if clinicians judge that patients have derived a meaningful response from somatostatin treatment (reduced stoma output, stool volume and progression towards closure of fistulas).

Summary of supporting evidence:

- Several meta-analyses have been published relating to the use of somatostatin analogues in enterocutaneous fistula. These studies have demonstrated positive effects of somatostatin analogues in fistula closure time and other secondary outcome measures.
- The safety profile of octreotide and lanreotide is well established and published studies relating to the proposed use have not raised any additional safety concerns.
- Somatostatin analogues provide an additional treatment option for patients with enterocutaneous fistula, high output stoma or refractory diarrhoea who have not fully responded to conservative management and other treatments (pharmacological or dietary).
- There is a lack of robust randomised controlled clinical trials data to support the use of somatostatin analogues in the proposed indications.

Details of Review

<p>Name of medicine (generic & brand name):</p> <p>Octreotide (Sandostatin, Sandostatin LAR[®]) and Lanreotide (Somatuline Autogel, Somatuline LA[®]) [1] [2]</p>
<p>Strength(s) and form(s):</p> <p>Octreotide:</p> <ul style="list-style-type: none">• 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] <p>Lanreotide:</p> <ul style="list-style-type: none">• 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]
<p>Dose and administration:</p> <p>Unlicensed use, dose based on those used across clinical studies:</p> <p>Chronic diarrhoea (short term treatment usually up to 30 days)</p> <ul style="list-style-type: none">• Octreotide 50-150 mcg two to three times daily• Octreotide long acting 30 mg monthly• Lanreotide 120 mg at baseline and day 28 <p>Enterocutaneous fistula</p> <ul style="list-style-type: none">• Octreotide 100 mcg three times daily• Lanreotide 30mg every 10 days <p>Stoma</p> <ul style="list-style-type: none">• Octreotide 50 to 100 mcg two to three times daily
<p>BNF therapeutic class / mode of action:</p> <p>Pituitary and hypothalamic hormones and analogues / somatostatin analogues which have a range of actions on various endocrine, neuroendocrine, exocrine and paracrine functions. [3]</p>
<p>Licensed indication(s)</p> <p>Octreotide - acromegaly, gastro-entero pancreatic endocrine tumours, complications following pancreatic surgery, bleeding gastro-oesophageal varices, treatment of TSH-secreting pituitary adenomas. [1]</p> <p>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]</p> <p>Please note that licensed indications vary between different formulations of octreotide and lanreotide. Please consult product SPCs for further information.</p>
<p>Proposed use (if different from, or in addition to, licensed indication above):</p>

Unlicensed use in secretory gastrointestinal disorders (e.g. enterocutaneous fistula, high output stoma and refractory diarrhoea).

Course and cost:

Octreotide (Sandostatin®): 50-150 mcg two to three times daily

Annual cost £2,171.02 to £9,756.45

Octreotide long acting (Sandostatin LAR®): 30 mg monthly

Annual cost (12 injections): £11,981.76

Lanreotide (Somatuline Autogel®): 120 mg every 28 days

Annual cost (12 injections): £11,244

Current standard of care/comparator therapies:

- For enterocutaneous fistula:
 - standard medical management focuses on sepsis control, wound care, and optimization of fluid, electrolyte, and nutrition status including parenteral nutrition. [4]
- High output stoma:
 - Reduced food intake/ parenteral nutrition.
 - Loperamide or codeine phosphate half an hour before food.
 - Proton pump inhibitors
 - Tricyclic antidepressants
 - Cholestyramine if bile salt malabsorption indicated.
- Refractory diarrhoea:
 - Similar to high output stoma treatment
 - Eluxadoline (irritable bowel syndrome with diarrhoea).

Relevant NICE guidance:

N/A

Background and context

Octreotide and lanreotide are synthetic analogues of somatostatin. They are useful in different conditions because they inhibit the endocrine and exocrine secretions associated with many diseases. Both drugs are licensed for use in a number of indications e.g. acromegaly, gastroenteropancreatic neuroendocrine tumours (GEPNETs), preventing complications after pancreatic surgery, and managing the emergency bleeding of gastro-oesophageal varices in patients with underlying cirrhosis. [5]

Historically, octreotide and lanreotide have also been used in the management of several unlicensed secretory gastrointestinal conditions including enterocutaneous fistula, high output stoma and refractory diarrhoea. National and International guidelines have advocated the use of somatostatin analogues in the management of enterocutaneous fistula and short bowel syndrome. [4] [6] The Individual Funding Requests team at the Midlands and Lancashire Commissioning Support Unit have received requests for the use of octreotide and lanreotide for the management of secretory gastrointestinal conditions. 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:

Enterocutaneous fistula

Three meta-analyses have assessed the effect of somatostatin analogues on enterocutaneous fistula (ECF) closure and mortality. The literature search did not identify any studies performed after the publication of these meta-analyses.

Rahbour et al Meta-analysis [7]

Nine RCTs comparing somatostatin and somatostatin analogues for use in the management of ECF were included in the study. For the somatostatin analogue trials there were 141 patients in the somatostatin analogue group and 147 in the control or placebo group. The authors assessed the methodological quality of the studies as “poor to moderate” using the GRADE system of appraisal. Dosages and duration of treatment varied across the trial although the use of somatostatin analogues was for short term use (over days or weeks rather than months).

The number of ECF closures was significantly greater in the somatostatin analogue group (n = 100/152) compared with the control group (n = 77/155) (RR = 1.36, [CI95% 1.12; 1.63], *P* = 0.002). ECF were significantly more likely to close faster with somatostatin analogues (n = 141) compared with the control (n=147) group (standardised mean difference = -0.51, [CI95% -0.75; -0.28], *P* < 0.0001). No significant difference in mortality was highlighted between analogues (n = 17/141) and controls (n = 21/147) (RR = 0.89, [CI95% 0.50; 1.56], *P* = 0.68).

Coughlin et al Meta-analysis [8]

Eight studies were included in this review of somatostatin analogues used to shorten time to closure of postoperative enterocutaneous fistula. The included studies were the same as the studies included in the meta-analysis by Rahbour et al [7] except for the omission of a single study which was not a randomised controlled trial.

There was a trend toward an increased incidence of closure in the somatostatin analogue group, but this failed to achieve significance (RR 1.28 [CI95% 0.94; 1.75], *P* = 0.12). A significant

decrease in the time to closure in the somatostatin analogue group was demonstrated (weighted mean difference = -6.37 days [CI95% -8.33; -4.42], $P < 0.00001$). There was a trend toward decreased mortality with somatostatin analogues; however, this was not statistically significant (RR = 0.87 [CI95% 0.49; 1.55] $P = 0.63$).

Stevens et al Meta-analysis [9]

Ten studies were included in the meta-analysis although three involved somatostatin. The studies relating to octreotide and lanreotide were the same studies as those considered in the meta-analyses by Rahbour et al [7] and Coughlin et al [8].

Spontaneous closure occurred in 55 out of 84 patients treated with octreotide and 43 out of 85 in the control groups (OR = 1.75 [CI95% 0.64; 4.75], $P = 0.279$), and 36 out of 54 lanreotide treated patients and 36 out of 53 control group patients (OR = 0.94 [CI95% 0.42; 2.12], $P = 0.89$). For octreotide, mean closure times were 15.5 (± 17.4) and 21.9 (16.9) days for controls. Closure times for lanreotide were 17 versus 26 days (SD not stated). Mortality ORs were 0.82 (CI95% 0.38; 1.78, $P = 0.62$) and 0.48 (CI95% 0.04; 5.47, $P = 0.555$) for octreotide and lanreotide respectively.

High output stoma (e.g. short bowel)

There is a lack of randomised controlled trials studying the use of somatostatin analogues in high output stoma. Five crossover RCTs conducted before 2007 were available but did not report data before the crossover therefore conclusions cannot be drawn from the data available from these trials. [5] One small randomised crossover trial of nine patients with an ileoanal pouch compared octreotide to placebo for effect on stool frequency. [10] No clear effect of octreotide on stool frequency was observed in patients with an ileoanal pouch. A guideline for the management of patients with a short bowel suggests that octreotide may be useful to reduce stomal output by one to two litres per 24 hours. [11]

Refractory diarrhoea

Refractory diarrhoea is defined as lasting more than 14 days and has failed to respond to specific treatment for a known aetiology or has failed to respond adequately to standard antidiarrhoeal preparations in conventional doses. [12]

The use of somatostatin analogues in chronic diarrhoea has been studied most extensively in patients with acquired immunodeficiency syndrome and post chemotherapy, however these uses are outside the scope of this new medicine review. A review of octreotide use in a small number of patients (5 studies comprising 21 patients demonstrated 16-72% reduction in intestinal output over 24 hours. The same review also assessed the long-term effects of octreotide in 3 studies comprising 8 patients. These studies demonstrated that reduced intestinal outputs were maintained when 100 mcg octreotide was administered over 24 hours. [12] In a controlled open-label prospective clinical trial of 33 patients with > three stools per day at baseline, lanreotide administered at baseline and day 28 experienced a significant decrease in the number of stools (5.7 at baseline to 3.7 at day 56, $P < 0.001$). [13]

Summary of safety data:

Safety data from studies relating to cohorts of patients with gastrointestinal secretory disorders is lacking. However, 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		
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 at treatment initiation;

The risk of bradycardia especially in patients with underlying cardiac problems.

Strengths and limitations of the evidence:

Strengths

- Several meta-analyses have been published relating to the use of somatostatin analogues in enterocutaneous fistula. These studies have demonstrated positive effects of somatostatin analogues in fistula closure time and other secondary outcome measures.
- The safety profile of octreotide and lanreotide is well established and published studies relating to the proposed use have not raised any additional safety concerns.
- Somatostatin analogues provide an additional treatment option for patients with enterocutaneous fistula, high output stoma or refractory diarrhoea who have not fully responded to conservative management and other treatments (pharmacological or dietary).

Limitations

- There is a lack of robust randomised controlled clinical trials data to support the use of somatostatin analogues in the proposed indications.
- The quality of evidence included in the meta-analyses relating to enterocutaneous fistula was assessed as poor quality due to the lack of reporting relating to blinding, randomisation etc.
- Available evidence reported variable dosing regimens with variable outcome measures. There was heterogeneity in both study designs and patient selection.
- There is a lack of additional safety data and quality of life data in the studies relevant to the proposed uses.

Summary of evidence on cost effectiveness:

N/A

Prescribing and risk management issues:

Based on the available published data, supportive evidence for the use of somatostatin analogues is primarily related to short term use (less than 30 days) and will require early clinical review following initiation.

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. **Invalid source specified.**

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 month (ex VAT)
Octreotide (Sandostatin [®])	50-150 mcg two to three times daily	£14.87 for 5 amps	£178 to £803
Octreotide long-acting (Sandostatin LAR [®])	10-30mg per month	30 mg = £998.41	£998
Lanreotide (Somatuline Autogel [®])	120mg per month	120 mg = £937.00	£937.00

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:

Enterocutaneous fistula, high output stoma and refractory diarrhoea represent a range of conditions causing important clinical problems which may adversely affect a patient's quality of life. When secretory outputs are still high despite the use other treatments, somatostatin analogues are additional treatment options to support the management of these conditions.

Financial implications of the intervention:

Based on a data provided by the Individual Funding Requests team at the MLCSU, it is anticipated that there will be no more than one or two requests for somatostatin analogues across the proposed uses per year.

Due to the nature of the conditions being treated it is anticipated that patients would be reviewed within one month of starting treatment. It is expected that continuation of treatment would only be recommended by clinicians if they judged that patients derived meaningful response from the treatment (reduced stoma output, stool volume and progression towards closure of fistulas). Greater Manchester Medicines Management Group (GMMMG) have set out continuation criteria following consultation with Gastroenterologists and it is anticipated that continuation criteria in Lancashire and South Cumbria will accord with these recommendations. [14]

The most commonly used preparation used in the clinical trials was standard octreotide injection:
Octreotide (sandostatin):

Monthly cost for 2 patients depending on dose = **£ 356 to 1606**

Annual cost for 2 patients = **£4,342 to £19,514**

<p>Should prescribers wish to prescribe long-acting preparations of octreotide the costs are as follows:</p> <p>Monthly cost for 2 patients depending on dose = £1196</p> <p>Annual cost for 2 patients = £23,962</p>
<p>Service Impact Issues Identified:</p>
<p>Although the use of octreotide/ lanreotide for secretory conditions would require additional monitoring it is not anticipated that their use would impact on the capacity in the healthcare system due to the small patient numbers affected. It would be expected that this cohort of patients would already be under the supervision of a specialist.</p>
<p>Equality and Inclusion Issues Identified:</p>
<p>Non-identified</p>
<p>Cross Border Issues Identified:</p>
<p>This LSCMMG draft guidance aligns with GMMMG guidance relating to the use of octreotide for the treatment of certain gastrointestinal conditions. Pan Mersey APC do not currently have a position on the use of octreotide/lanreotide in the management of secretory gastrointestinal disorders.</p>
<p>Legal Issues Identified:</p>
<p>N/A</p>
<p>Media/ Public Interest:</p>
<p>N/A</p>

References

References

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- [5] G Murphy et al, "Octreotide for Endocrine, Oncologic, and Gastrointestinal Disorders: Systematic Review and Budget Impact Analysis," *Canadian Agency for Drugs and Technologies in Health*, p. Technology overview number 45, 2008.
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- [14] Greater Manchester Medicines Management Group, "Octreotide for treatment of certain gastrointestinal indications," January 2018. [Online]. Available: <http://gmmmg.nhs.uk/docs/nts/Octreotide-gastro-recommendation.pdf>. [Accessed 13 November 2019].

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • consensus guidelines • expert opinion • case series 	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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