New Medicine Assessment

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

Unlicensed use in non-acute treatment of recurrent gastrointestinal bleeding disorders (including angiodysplasia, small bowel dysplasia, gastric antral vascular ectasia, haemorrhagic telangiectasia)

Recommendation: Red

Octreotide and lanreotide are recommended for the non-acute treatment of recurrent gastrointestinal bleeding disorders. 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.

Treatment should only be continued if an adequate response is achieved (e.g. a 50% reduction in the need for transfusion or parenteral iron).

Summary of supporting evidence:

- The included studies demonstrate a long history of real-world somatostatin analogue use to prevent recurrent GI bleeding with all published studies demonstrating a benefit.
- 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.
- For patients where endoscopic treatment is unsuitable/not possible or has failed, octreotide/lanreotide offer an additional treatment option.
- Long-acting preparations enable monthly dosing for lanreotide and octreotide.
- There is a lack of robust randomised controlled clinical trials data to support the use of octreotide to prevent recurrent GI bleeding or studies with robust statistical analysis of outcome data.

Date: October 2019

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 10-30 mg monthly

Octreotide 50–100 mcg two or three times daily

Lanreotide long acting 60-90 mg every 28 days

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 based on the costs stated in the October 2019 NHS Electronic Drug Tariff:

Octreotide long acting (Sandostatin LAR®): 10-30 mg monthly

Annual cost (12 injections): £6,596.52 to £11,981.76

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

Annual cost £2,171.02 to £6,125.43

Lanreotide (Somatuline Autogel®): 60-90 mg every 28 days

Annual cost (12 injections): £6,612 to £8,832

Current standard of care/comparator therapies:

- Endoscopic procedures and surgery (e.g. argon plasma coagulation, sclerotherapy, ligation etc) in suitable patients.
- Unlicensed pharmacological treatments (the antiangiogenic drug thalidomide has been trialled in angiodysplasia and hormonal-based therapy in hereditary haemorrhagic telangiectasia). [4]

Relevant NICE guidance: N/A

Background and context

Vascular malformations of the gastrointestinal (GI) tract are responsible for 2-8% of all cases of bleeding and 30-40% of all obscure haemorrhages, being the most frequent cause of occult bleeding in the elderly. [5]

Various classifications of vascular malformations have been proposed including Hereditary Haemorrhagic Telangiectasia, Blue Rubber Bleb Nevus Syndrome, angiodysplasia, hypertensive gastropathy, gastric antral vascular ectasia (GAVE), Dieulafoy's lesion and varices. Angiodysplasias are the most common gastrointestinal vascular abnormalities and are the first cause of bleeding from the small bowel in people over the age of 60. Symptoms related to these lesions can be caused by both acute haemorrhages, associated to haematemesis, melaena or haematochezia, and chronic bleeding, inducing iron deficiency anaemia. Moreover, because the endoscopic diagnosis of the source of bleeding can be difficult, especially for small bowel lesions, it can be delayed for a long period after the initial onset of symptoms. [5]

First-line therapy is endoscopy (Argon Plasma Coagulation, endoscopic clips, endoscopic band ligation, laser photocoagulation). Angiographic embolisation and surgical resection are additional treatment options, but they may be associated with rebleeding episodes, mostly due to the presence of multiple lesions. Moreover endoscopic, radiological and surgical therapies cannot be performed in patients with significant comorbidities, nor when the source of bleeding is not identified. [5]

In this difficult-to-treat patient setting, various drugs have been proposed and studied. Octreotide (and lanreotide), an analog of somatostatin, can act in both acute and chronic bleeding from digestive vascular malformations through different mechanisms: downregulation of VEGF levels, reduction of splanchnic blood flow, increasing vascular resistance and improving platelet aggregation. [5]

The Individual Funding Requests team at the Midlands and Lancashire Commissioning Support Unit have received several requests for the use of octreotide and lanreotide for the management of recurrent GI bleeding. 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 is a single randomised controlled trial investigating the use of octreotide/lanreotide for the non-acute management of recurrent bleeding by **Jenkins et al** [6]. Thirty two patients with cirrhotic portal hypertension were randomly allocated treatment with either 6 months of combination sclerotherapy and octreotide 50 mcg subcutaneously twice daily or sclerotherapy alone. The primary outcome of the trial was the number of episodes of recurrent variceal bleeding and survival.

Significantly fewer patients receiving combined octreotide and sclerotherapy had episodes of recurrent variceal bleeding compared with patients given sclerotherapy alone (1/16 *v* 7/16; P = 0.037). During the 6 months of the trial 5 patients died, all in the group receiving sclerotherapy alone; 4 died after recurrent variceal bleeding. At the end of the trial patients receiving the combined treatment showed a significant improvement in survival compared with those receiving sclerotherapy alone (P < 0.02), and this was maintained for 12 further months, but no longer.

Other efficacy data:

Other studies in literature reported only small numbers of enrolled patients (202 patients in total in the included studies), heterogeneous therapeutic schedules and short-term follow-up. As a result, the use of octreotide/lanreotide is not approved for this purpose and it is currently still prescribed as an off-label drug. [5] The results of the observational studies for the use of octreotide and lanreotide are reported below.

Frago et al [6]

A retrospective study of 27 patients with gastrointestinal angiodysplasia bleeding and obscure gastrointestinal bleeding. Patients were treated with 60-90 mg of lanreotide every 28 days for at least 6 consecutive months and measured for response where complete response was defined as a lack of new blood transfusion or endovenous iron doses needed after beginning lanreotide. Partial response was considered when the need for transfusion or endovenous iron decreased more than 50% with respect to what was observed throughout the reference year, without a related rise in the other therapy. Finally, response in admission was understood as more than 50% reduction in admission days.

The bleeding was attributable to angiodysplasia in 85.2%, of whom half had multi-site lesions. Lanreotide was administered for a median of 27.1 months. During follow-up of up to 3 years (mean 32.5 months), 18.5% of patients achieved complete response and around 60% a 50% reduction of health resource consumption.

G Nardone et al [7]

This retrospective study of 98 patients with a history of bleeding due to gastrointestinal angiodysplasias was performed over 2 years. All patients had received octreotide 0.1 mg three times daily for 28 days and, then from day 14, long acting release-octreotide 20 mg monthly, for 6 months. Response to treatment was measured with the following definitions: “full responders”: patients who, after the first cycle of therapy, did not have overt bleeding and had stable haemoglobin levels during follow-up; “relapsers”: patients who, after up to three cycles of therapy, did not have overt bleeding and had stable haemoglobin levels during follow-up; “poor responders”: patients who, despite continuous octreotide treatment, had overt bleeding or low haemoglobin levels that required supportive therapy during follow-up.

According to the outcome and timing of response to therapy patients were classified as follows: 40 full responders (41%); 32 relapsers (33%); 26 poor responders (26%). Among the 32 relapsers, 21 patients underwent 2 cycles and 11 patients 3 cycles of LAR-octreotide treatment.

C Bon et al [8]

An observational pilot study of 15 consecutive patients with recurrent bleeding from gastrointestinal angiodyplasia was performed for 6 months. If, despite appropriate treatment, bleeding and/or severe anaemia recurred and the number of blood units exceeded 5, within 3 months, the case was considered refractory and additional treatment with long-acting somatostatin analogue was administered for a minimum of 6 months (octreotide-LAR, LAR Sandostatin, 20 mg monthly intramuscularly or lanreotide, Somatulin 90 mg, every 28 days).

The median duration of somatostatin analogue treatment was 12 months (range: 6–36). The number of transfusions significantly decreased in the period during treatment compared with the 6 month period before [median number: 2 (0–14) vs. 10 (6–24); P < 0.001]. The percentage of patients who experienced a bleeding event was lower during somatostatin analogues treatment (20% vs. 73%; P = 0.01). The mean haemoglobin level was significantly higher when somatostatin analogues were offered [median: 10 g/dL (9–13) vs. 7 (5–8.5); P < 0.001].

G Scaglione et al [9]

This single centre uncontrolled study observed 13 patients with chronic GI bleeding because of multiple upper and/or lower angiodysplasia defined by iron deficiency anaemia with repeated positive faecal occult blood test and angiodysplasias in the GI tract. Long acting octreotide (Sandostatin LAR) was intramuscularly administered to all patients at a dosage of 10 mg/ monthly for 1 year. The primary end point was the presence of normal Hb values (>12 g ／ dL) with repeated negative faecal occult blood test at 1 year after the start of treatment.

Follow-up ranged from 12 to 60 months. Nine of 13 patients (69%) did not need blood transfusions and iron supplementation any longer; a partial improvement was observed in one patient; no effect was found in the others.

F Junquera et al [11]

A prospective cohort study of 32 patients diagnosed with bleeding from angiodysplasia was treated with octreotide 50 mcg every 12 h subcutaneously for a 1–2-year period. This cohort was compared with an external control group (38 patients who had received placebo [1 tablet/day] in a concurrent randomised clinical trial for the same period. The primary end point was failure of treatment defined as the presence of any episode of acute gastrointestinal bleeding, or chronic gastrointestinal bleeding with positive faecal occult blood test and ferropenic anaemia with haematocrit below 26% or haematocrit below 30% despite continuous iron therapy for 6 months.

Two patients of the octreotide group were lost to follow-up. Treatment failure occurred in seven of 30 (23%) patients in the octreotide group and in 17 of 35 (48%) in the placebo group (three dropouts before first visit) (*P* = 0.043). The actuarial probability of remaining free of rebleeding at 1 and 2 year of follow-up was 77% and 68%, respectively, for the octreotide group and 55% and 36%, respectively, for the placebo group (log rank *P* = 0.030).

G Nardone et al

In this observational study, 17 patients with a history of chronic and/or acute GI bleeding (requiring several blood transfusions and repeated cycles of iron therapy) were treated with octreotide 0.1 mg three times daily for 6 months. The efficacy of therapy was evaluated by the monitoring of haemoglobin levels and the need for blood transfusions or iron therapy.

Following octreotide treatment the average haemoglobin level increase was from 5.7 to 11.1 g/dL (P < 0.0005), while blood units transfused decreased from an average of 8.8 to 1.5 units per year (P < 0.0005). Octreotide was successful in 10 subjects, who therefore no longer required iron supplementation. A transient improvement was obtained in four patients. No effect was observed in three who required recurrent cycles of iron therapy and blood transfusions.

Summary of safety data:

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. The adverse events reported in the studies are in line with the safety data listed in the SPCs for octreotide and lanreotide. 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

- The included studies demonstrate a long history of real-world somatostatin analogue use to prevent recurrent GI bleeding with all publish studies demonstrating a benefit.
- 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.
- For patients where endoscopic treatment is unsuitable/not possible or has failed, octreotide/lanreotide offer an additional treatment option.
- Long-acting preparations enable monthly dosing for lanreotide and octreotide.

Limitations

- There is a lack of robust randomised controlled clinical trials data to support the use of octreotide to prevent recurrent GI bleeding or studies with robust statistical analysis of outcome data.
- Most studies were not randomised and only included small numbers of patients without a control group for no longer than 12 months.
- The doses used and treatment/follow up periods varied considerably across the observational studies.
- Much of the data relates to angiodysplasia. There was a lack of supporting data for the management of hereditary haemorrhagic telangiectasia and gastric antral vascular ectasia.

Summary of evidence on cost effectiveness:

One study has been carried out relating to the cost effectiveness of long-acting octreotide in the treatment of GI bleeding due to vascular malformations. [12] This study was in the Spanish health economy and used data from 19 patients that were treated with monthly injections of long acting octreotide between 2008-2013. The number of blood transfusions, haemoglobin levels, hospital admissions and possible side effects during the year before treatment and the year after the start of the treatment were assessed, and cost-effectiveness was analysed.

After the beginning of the treatment with long-acting octreotide, complete response was observed in 7 patients (36.8 %), partial response in 7 patients (36.8 %) and 5 patients (26.3 %) continued to require admissions, blood transfusions and/or endoscopic treatment. Significant reduction was observed in the length of admission per year (in days) before and after the start of the treatment (22.79 *versus* 2.01 days, $p < 0.0001$) as well as in the number of blood transfusions administered (11.19 *versus* 2.55 blood transfusions per year, $p = 0.002$). The mean haemoglobin levels increased from 6.9 g/dl to 10.62 g/dl ($p < 0.0001$). Cost reductions of 61.5 % were observed

between the two periods (from 36,072.35 € to 13,867.57 € per patient and year, p = 0.01).

Prescribing and risk management issues:

The long acting preparations of lanreotide are administered by subcutaneous injection and long acting preparations of octreotide are administered by deep intramuscular 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 long-acting (Sandostatin LAR®)	10-30 mg monthly	10 mg = £549.71 20 mg = £799.33 30 mg = £998.41	£6696.52 to £11,981.76
Lanreotide (Somatuline Autogel®)	60-90 mg every 28 days	60 mg = £551.00 90 mg = £736.00	£6,612 to £8,832 (12 injections)
Octreotide (Sandostatin®)	50-100 mcg two to three times daily	50 mcg = £2.97 100 mcg = £5.99	£2,171.02 to £6,125.43
Costs based on Electronic Drug Tariff list prices October 2019. This table does not imply therapeutic equivalence of drugs or doses.			

Innovation, need and equity implications of the intervention:

For patients where endoscopic treatment is unsuitable/not possible or has failed, octreotide/lanreotide offer an additional treatment option. Currently treatment options are limited for this cohort of patients.

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 recurrent GI bleeding disorders across Lancashire and South Cumbria between January 2017 and August 2019. This equates to 2 or 3 patients per year across Lancashire and South Cumbria.

If 3 patients were treated with the highest dose of long-acting octreotide (most expensive permutation) the annual acquisition cost would be as follows:

3 X £11,981.76 = **£35,945.28**

If 2 patients were treated with the lowest dose of lanreotide (least expensive permutation) the annual acquisition cost would be as follows: 2 X £6,612 = **£13,224** 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. an endoscopic intervention or 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 recurrent GI bleeding 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:
Non-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 recurrent GI bleeding disorders. 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

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[3] Joint Formulary Committee, "BNF (online)," London: BMJ Group and Pharmaceutical Press, [Online]. Available: http://www.medicinescomplete.com. [Accessed 18 October 2019].

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[5] A Iannone et al, "Gastrointestinal bleeding from vascular malformations: Is octreotide effective to rescue difficult-to-treat patients?," *Clinics and Research in Hepatology and Gastroenterology,* vol. 40, pp. 373-377, 2016.

[6] SA Jenkins et al, "Randomised trial of octreotide for long term management of cirrhosis after variceal haemorrhage," *British Medical Journal,* vol. 315, pp. 1338-1341, 1997.

[7] S Frago et al, "Long-term results with lanreotide in patients with recurrent gastrointestinal angiodysplasia bleeding or obscure gastrointestinal bleeding. Benefits in efficacy and procedures consumption," *Scandinavian Journal of Gastroenterology,* vol. 53, no. 12, pp. 1496-1509, 2018.

[8] G Nardone et al, "Long acting release-octreotide as "rescue" therapy to control angiodysplasia bleeding: A retrospective study of 98 cases," *Digestive and Liver Disease,* vol. 46, pp. 688-694, 2014.

[9] C Bon, "Long-acting somatostatin analogues decrease blood transfusion requirements in patients with refractory gastrointestinal bleeding associated with angiodysplasia," *Alimentary Pharmacology and Therapeutics,* vol. 36, pp. 587-593, 2012.

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[11] F Junquera et al, "Long-Term Efficacy of Octreotide in the Prevention of Recurrent Bleeding from Gastrointestinal Angiodysplasia," *American Journal of Gastroenterology,* vol. 102, pp. 254-260, 2007.

[12] K Klimova et al, "Octreotide long-active release in the treatment of gastrointestinal bleeding due to vascular malformations: Cost-effectiveness study," *Revista Espanola De Enfermedades Digestivas,* vol. 107, no. 2, pp. 79-88, 2015.

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