Oxford University Hospitals NHS
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Clinical Commissioning Group

# Somatostatin Analogue treatments in Neuroendocrine Tumours
# Shared Care Protocol

**This protocol provides prescribing and monitoring guidance for Somatostatin Analogue therapy in the treatment of Neuroendocrine Tumours. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc , the BNF and the Shared Care Protocol Responsibilities.**

## Background for Use

Neuroendocrine tumours (NETs) are rare and include bronchial, hindgut and midgut carcinoid tumours, pancreatic islet cell tumours, medullary thyroid carcinoma, paragangliomas and phaeochromocytomas. In the UK, approximately 3000 patients are diagnosed with these tumours every year. The World Health Organisation (WHO) classification defines NETs according to their site, and whether or not they are functional, including the type of peptide secreted. Types of tumour:

*Gastro-entero-pancreatic NETs*

These are the commonest type of NET, with an incidence of about 30 new cases per million of population per year, and accounts for 55% of all NETs. The tumours may arise in the foregut (stomach, pancreas and lung), midgut (ileum, appendix) or hindgut (distal colon, rectum and genitourinary tract). They are often slow-growing indolent tumours with low potential for metastasis, but always have the potential for metastatic spread and can occasionally be rapidly progressive. They may produce peptides such as serotonin, tachykinins, histamines and prostaglandins. These peptides are responsible for the characteristic symptoms of carcinoid syndrome (diarrhoea, flushing, wheezing, and heart disease). The likelihood of a tumour producing these peptides is highest with midgut tumours, intermediate in foregut tumours and lowest in hindgut tumours.

Pancreatic (islet cell) NETs may be functioning (hormone-secreting) or non-functioning. Non-functioning tumours are more common and present with mass effects. They are sometimes mistaken for pancreatic adenocarcinoma. The commonest functioning tumours secrete insulin or gastrin, but a whole range of other hormones may be secreted.

*Multiple endocrine neoplasia type 1 (MEN 1)*

Some NETs arise as part of a genetic disorder, especially MEN 1, in which primary hyperparathyroidism, pituitary tumours and pancreatic tumours are the commonest tumours, but also a range of other genetic disorders.

## Diagnosis

NETs are often discovered because of their mass effects such as bowel obstruction, production of hormones (e.g., carcinoid syndrome with flushing or diarrhoea; hypoglycaemia symptoms with insulinomas, etc), or as an incidental finding at operation, or on scanning for other reasons.

## Diagnostic tests

Biochemical tests include fasting gut hormones, plasma chromogranins A and B, and urinary 5-HIAA. Staging of the tumour is required using imaging, for instance with CT or MRI, or with

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Verified by Sara Wilds Medicines Management Team & Sarah Poole Clinical Pharmacist OUH Version 2 January 2012
Version 3: Updated by Professor Ashley Grossman and Mike Tadman, Endocrinology OUH. Approved by APCO September 2016. Review date: September 2018
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radioisotope scanning, e.g., octreotide. Histopathology should be undertaken to establish a tissue diagnosis whenever possible.

**Treatment options**
Unfortunately, there is no single treatment that is universally effective. A number of options are available to reduce tumour burden and improve symptoms. The choice will depend upon the extent of the tumour, its stage, and the effects of the tumour and its secretions on the patient. The Neuroendocrine team uses a multidisciplinary approach.

*Surgery*
Surgery is often possible and aims to cure the disease or reduce the tumour load significantly. However, surgery may not be an option, usually because the disease is widespread with multiple metastases, although even then removal of the primary may be attempted as in some studies this has been shown to improve survival. In addition, removal may decrease the risk of intestinal obstruction. Such surgery may also include hepatic metastatectomy or partial hepatectomy.

*Radionuclide therapy*
This may be of benefit in patients with positive radionuclide (MIBG or octreotide) scans. Response rates of up to 60% have been reported for metastatic NETs of any site of origin. Recently, the use of Yttrium-90 DOTA octreotide and Lutetium-177-DOTATATE-octreotide have shown considerable promise, with a randomised trial favouring Lutetium-177-DOTATATE-octreotide over simply increasing the dose of octreotide.

*Chemotherapy*
This is usually reserved for foregut NETs, including bronchial carcinoids and pancreatic NETs, although the best regimen is as yet unclear. Clinical trials are in progress to evaluate the role of chemotherapy for midgut and hindgut NETs. Currently, for grade 1 and 2 NETs the optimal chemotherapy appears to be capecitabine in combination with either streptozotocin or temozolomide. For poorly-differentiated or grade 3 tumours, etoposide and a platinum are usually used first-line.

*Radiotherapy*
NETs tend not to be very radiosensitive but radiotherapy may be of benefit for patients with bone metastases.

*Hepatic artery embolisation*
Embolisation can be effective in reducing tumour load and hence symptoms. The treatment has the aim of cutting off the blood supply to the tumour. Side effects include those of tissue necrosis and release of hormones from necrotic tumour tissue. Embolisation can be bland, utilise chemotherapeutic agents, or radiolabelled spheres (SIRT), with no clear evidence favouring one approach over another.

*Radio-frequency ablation*
This may be effective in reducing tumour load and reducing symptoms. Tumour necrosis with the resultant release of hormones and peptides may precipitate a carcinoid crisis and hence this treatment, like embolisation, is undertaken only in specialist centres.

*Targeted therapies*

Recent large-scale randomised trials have clearly shown a reduction in the rate of progression of pNETS with sunitinib, and for all types of NETs, especially pNETS, with the mTOR inhibitor everolimus.

**Supporting Information**

Somatostatin was discovered because of its effect of inhibiting growth hormone secretion by the pituitary. It has been used in this role for some years. Many NET cells also have somatostatin receptors, and treatment with somatostatin analogues often has beneficial effects in reducing symptoms from the carcinoid or other functional syndrome, and has now been shown to slow tumour progression even in asymptomatic patients.[1,2] This has been clearly demonstrated for both pancreatic and mid-gut NETs, and probably other NETs from various sites.[1,2]

**Contraindications and Precautions**

| **Adverse Reactions** | |
|---|---|
| Summary<br>The adverse reactions related to Somatuline Autogel and Sandostatin LAR during clinical trials are consistent with those seen with other prolonged release formulations of lanreotide or octreotide, and are predominantly gastrointestinal. More than 50% of adverse events were classified as gastrointestinal system disorders. The most commonly reported adverse reactions are diarrhoea, abdominal pain and nausea. These reactions are usually mild and transient. | |
| *Very common adverse reactions* (more than 10% of patients | Diarrhoea, abdominal pain, nausea. |
| *Common adverse reactions*: (more than 5% but less than 10% of patients) | Constipation, flatulence, cholelithiasis, gall bladder sludge. |
| *Less common adverse reactions*: ( between 1 and 5% of patients | Asthenia, fatigue, increased bilirubin. |
| *Uncommon adverse reactions*: (less than 1% of patients). | Injection site pain, skin nodule, hot flushes, leg pain, malaise, headache, tenesmus, vomiting, abnormal glucose tolerance, hyperglycaemia, decreased libido, somnolence, pruritus, increased sweating, alopecia. |
| *Local tolerance* | Reactions at the injection site may occur after the deep subcutaneous injection of Somatuline Autogel in the buttock. When specific enquiry was made, pain, redness, itching and induration were reported at the injection site 30 minutes after dosing in up to 8%, 5%, 5% and 19% of patients respectively. After 3 dosing intervals, these symptoms or signs were reduced to 6%, 2% |

| | |
|---|---|
| | 3% and 9% of patients or fewer. In all cases, the symptoms were described as mild. |
| *Contra-indications/Cautions* | Hypersensitivity to Sandostatin, lanreotide or related peptides or any of the excipients listed in SPC |
| Pregnancy and lactation (if appropriate) | This drug should be used during pregnancy only if clearly needed. |
| N.B. Drug interactions (refer to BNF or SPC; include significance of interaction). | |

**Dosage**

| **Dosage & Indications** | |
|---|---|
| Sandostatin LAR | Indication:<br>The treatment of symptoms associated with neuroendocrine (particularly carcinoid) tumours.<br>Advanced neuroendocrine tumours of the midgut or of unknown primary origin |
| Starting Dose: 20-30mg every 28 days. | Maximum Dose: 30 mg every 21-28 days |
| Somatuline Autogel | Indication:<br>The treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) GEP-NETs of midgut, pancreatic or unknown origin.<br>The treatment of symptoms associated with neuroendocrine (particularly carcinoid) tumours. |
| Starting Dose: 90-120mg every 28 days usually for 3 months | Maximum Dose: 120 mg every 21-28 days |
| N.B. The dose is subsequently adjusted according to symptom benefit, side-effect and disease response | |

**Time to Response**

Response for patients with carcinoid syndrome, e.g. flushing and/ or diarrhoea is normally seen within a matter of a few days. Tumour stabilization can be seen within a few months and is monitored through regular CT and or MRI imagining.

**Pre-Treatment Assessment and first injection**

In Oxford, within our Neuroendocrine tumour team, we usually commence treatment as a day case. At present, we use both long-acting analogues; lanreotide is given subcutaneously and may be administered by the patient or their carer; however, most clinical trial information has come from studies with octreotide LAR[1,2]. Therapy is usually initiated by the Senior Specialist Neuroendocrine Nurse, who will give a single injection of a long-acting preparation.

**Future injections**
Subsequent doses are usually given by the general practice team who will be shown how to give the injections by a specialist nurse from the homecare team. The medication will be delivered directly to the GP surgery via the homecare team, to ensure compliance with cold chain issues. The patient will attend the surgery on the agreed day of injection every 28 days. Please note that the injection must be at room temperature (out of fridge for 30-60 minutes) prior to administration. For patients who can't easily attend the surgery the homecare nurses can arrange training for district nurses. This will only be for a few patients with advanced disease, who may well have district nurse input already.

There is an option for self-administration using Somatuline Autogel, and also for a family member to administer the drug to the patient. This is discussed with patients at their day case appointment at OCDEM when the drug is commenced. Training for self/family administration is provided by specially trained homecare nurses.
N.B. This option is not available for Sandostatin LAR.

**Ongoing Monitoring**
The patient is followed clinically by the neuroendocrine multidisciplinary team based at the Churchill Hospital. The response to treatment is assessed by monitoring clinical symptoms, hormone output and also by radiological imaging. The aims of treatment are to reduce the patient's symptoms, normalise the hormone parameters and to stabilise disease. We will also monitor for side effects, e.g. changes in liver function and possible development of gallstones. We will tell the general practice team about any necessary dosage alterations. If the patient fails to respond to treatment, or side effects of the treatment become difficult to manage, it may be discontinued. If there is suspected development of gallstones, this will be monitored by ultrasound of the gallbladder, arranged at the Churchill Hospital. Dose reduction in diabetic medication may be necessary. If non-urgent side effects occur or are suspected, then you can contact the Senior Specialist Neuroendocrine Nurse for advice (see phone numbers below). If more urgent advice is required then please call the on-call endocrine or oncology registrar via the Churchill switch board.

The patient needs to see the GP practice nurse for monthly injections and to come to the hospital for assessment of response to treatment and tumour progression, for monitoring ultrasound of gallbladder and for outpatient appointments.

**Actions to be taken**

*Responsibilities of GP/practice nurse*
The GP/practice nurse will administer the injection of the long acting somatostatin analogue, following training from the specialist nurse from the homecare team if required. They will also monitor for any immediate adverse effects, e.g., excessive pain or irritation at the injection site or signs of infection. The injection sites should be rotated to minimise pain and irritation. Other possible side effects include anorexia, nausea, vomiting, abdominal pain, bloating, flatulence, diarrhoea, and steatorrhoea. Advice on managing these can be obtained from the Senior Specialist Neuroendocrine Nurse (see overleaf). Any persistent or severe side effects should be reported to the patient's neuroendocrine team, which will be responsible for any alterations in dosage or advice about alternative or additional medication. Blood glucose monitoring may occasionally be required if symptoms of hyperglycaemia occur. Please

contact the Senior Specialist Neuroendocrine Nurse if you have any concerns or questions regarding on-going monitoring.

*Responsibilities of Neuroendocrine team*
The Neuroendocrine team will be responsible for prescribing the medication and delivery via the homecare team. They will also monitor the patient's side-effects, progress and responsiveness at regular clinical assessments, plus monitoring of blood tests and relevant radiological and, where appropriate, radionuclide scanning. The GP will be required to monitor for the side effects noted above.

*Responsibilities of the patient*
The patient is required to attend at the appropriate time and place for the administration of the medication. They should also notify the Neuroendocrine or GP team of the development of side-effects or medical concerns. They also need to attend regular clinic appointments as notified by the Neuroendocrine team.

**Notable Drug Interactions**

Refer to BNF and SPC

**Back-up Information and Advice**

| **Contact Details** | | |
|---|---|---|
| Name | Telephone | Email |
| Dr A. Weaver | 01865 235209 | Andrew.weaver@ouh.nhs.uk |
| Dr B. Jafar-Mohammadi | 01865 (2)27 424 | bahram.jafar-mohammadi@nhs.net |
| Mike Tadman (Senior Specialist Neuroendocrine Nurse | 01865 572348 (or bleep 5138 via Churchill Hospital switchboard) | mike.tadman@nhs.net |
| Catherine Chaytor, Senior Oncology Pharmacist | 01865 235217 | Catherine.chaytor@ouh.nhs.uk |

**References**

1- Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M et al. Placebo-controlled, double blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009; 27(28):4656-4663.

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