NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Lanreotide for treating unresectable locally advanced or metastatic gastroenteropancreatic neuroendocrine tumours without disease progression

Draft scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of lanreotide within its marketing authorisation for treating unresectable locally advanced or metastatic gastroenteropancreatic neuroendocrine tumours without disease progression.

Background

Neuroendocrine tumours constitute a heterogeneous group of rare tumours. These tumours develop from neuroendocrine cells of the pancreas, gastrointestinal tissue (from diffuse neuroendocrine cells distributed throughout the gut), lung, and thyroid. Depending on the data source used, approximately 45-65% of neuroendocrine tumours occur in the gastrointestinal tissue and approximately 3-7 % in the pancreas. Neuroendocrine tumours can be broadly subdivided into those with and those without a clinical syndrome and are accordingly termed 'functional' or 'non-functional' neuroendocrine tumours, respectively.

Neuroendocrine tumours can be graded as low (grade 1), moderate (grade 2) or high grade tumours (grade 3) based upon how the tumour cells look under the microscope. The grade of tumour gives an idea of how quickly the tumour may develop. The tumours can also be referred to as 'well differentiated' (corresponding to grades 1 and 2), and poorly differentiated tumours (grade 3). Ki-67 proliferative index (Ki-67 index) is also used as a prognostic measure for grading parameters for neuroendocrine tumours. Grade 1 is equivalent to a Ki67 index of up to 3%, Grade 2 is equivalent to a 3-20%. Ki67 index beyond a score of 20% is equivalent to grade 3. The stage of the tumour describes its size, with advanced neuroendocrine tumours falling within stages III (locally advanced and/or has spread to regional lymph nodes) and IV (distant metastasis has occurred). The 5 year survival rate for stages III and IV range from 55% to 79%[1].

Neuroendocrine tumours of the gastrointestinal tissue are classified according to their point of origin, into tumours of the foregut (stomach, gall bladder, and proximal duodenum), midgut (distal duodenum, jejunum, ileum, caecum and appendix ascending, and right two thirds of transverse colon) and hindgut (left one third of transverse colon, descending colon, sigmoid colon and rectum). The incidence of neuroendocrine tumours of the gastrointestinal tissue may be between 2 and 3 per 100,000 of the population per year[1]. Most

neuroendocrine tumours of the gastrointestinal tissue are non-functioning and are associated with non-specific symptoms such as intestinal or bronchial obstruction and abdominal pain. A specific clinical syndrome related to these tumours is carcinoid syndrome which is caused by the tumour secreting serotonin. Symptoms include flushing, diarrhoea, heart palpitations and congestive heart failure. Neuroendocrine tumours of the gastrointestinal tissue are usually slow growing and survival depends on a number of factors such as histological type, degree of differentiation, tumour size and presence of liver or lymph node metastases.

Pancreatic neuroendocrine tumours (also known as pancreatic islet cells tumours) develop from pancreatic islet cells. The incidence of pancreatic neuroendocrine tumours is estimated to be less than 0.2 per 100,000 of the population per year[1]. The incidence of pancreatic neuroendocrine tumours is age-related. Functioning tumours constitute approximately 25-50% of all pancreatic neuroendocrine tumours, with insulinoma (produces too much insulin) and gastrinoma (produces too much gastrin) as the most common. Presentation and symptoms of functioning pancreatic neuroendocrine tumours include severe peptic ulceration, diarrhoea, confusion, sweating, dizziness, weakness, high blood pressure, skin rashes, anaemia and mouth ulcers. Non-functioning tumours generally present with mass effects of the primary tumour or metastases of the liver.

Surgery is the only curative treatment for neuroendocrine tumours of gastrointestinal or pancreatic origin. For people who are unable to have surgery, or where surgery has been unsuccessful or curative surgery was not an option because of the advance stage of the disease, the choice of treatment depends on the symptoms, stage of disease, and histological features of the tumour. Somatostatin analogues such as lanreotide (as Somatuline Autogel) and octreotide (long-acting release formulation) are used for treating unresectable locally advanced or metastatic tumours that have not progressed. Other treatment options for this stage of disease may include watchful waiting alongside treatment of the symptoms caused by the tumour. Symptomatic treatment depends on whether the tumours are functioning or non-functioning and if functioning, which hormone is being secreted.

This technology appraisal only considers lanreotide for the treatment of neuroendocrine tumours of gastrointestinal or pancreatic origin without disease progression. Lanreotide for the treatment of neuroendocrine tumours of gastrointestinal or pancreatic origin with disease progression is outside the scope of this appraisal and is subject to another ongoing NICE appraisal (ID858).

The technology

Lanreotide (Somatuline Autogel, Ipsen) is a short peptide analogue of a hormone called somatostatin and inhibits the release of many different types of hormones. The exact mechanism of action of lanreotide in delaying

progression of gastroenteropancreatic neuroendocrine tumours is not known. Lanreotide is administered by deep sub-cutaneous injection.

Lanreotide has a marketing authorisation in the UK for treating 'grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of mid-gut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease'.

Intervention(s)	Lanreotide
Population(s)	Adults with either grade 1 or grade 2 with Ki67 index up to 10%, unresectable locally advanced or metastatic gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded **and** • whose disease has not progressed[*]
Comparators	For gastrointestinal neuroendocrine tumours • octreotide (long-acting release formulation) For pancreatic neuroendocrine tumours • watchful waiting and symptomatic treatment (including but not restricted to somatostatin analogues)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • symptom control • adverse effects of treatment • health-related quality of life

[*] Lanreotide for the treatment of neuroendocrine tumours of gastrointestinal or pancreatic origin with disease progression is subject to another ongoing NICE appraisal [ID858].

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows the following subgroups will be considered: • location of tumour • stage of tumour • secretory profile Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Appraisals in development 'Everolimus, lanreotide, lutetium-177 and sunitinib for treating unresectable or metastatic neuroendocrine tumours with progressed disease'. NICE technology appraisal guidance [ID858], Anticipated date of publication August 2017. 'Lutetium-177 DOTATATE for treating inoperable, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours without disease progression'. NICE technology appraisal guidance [ID 857], Publication date to be confirmed. Related Guidelines: 'Diagnosis and management of metastatic malignant disease of unknown primary origin' (2010) NICE guideline 104. Static guidance Related NICE Pathways: Metastatic malignant disease of unknown primary origin overview (2010) NICE pathway http://pathways.nice.org.uk/metastatic-malignant-disease-of-unknown-primary-origin

Related National Policy	NHS England commissions adult specialist endocrine services from Adult Specialist Endocrinology Centres for specified condition, including the management of neuro-endocrine tumours of the gut and elsewhere (see section 10. Adult specialist endocrinology services, pages 37-38) http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1, 4 and 5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

Reference

1. Ramage J et al. (2012). Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs) Gut 61: 6–32.

Questions for consultation

Have all relevant comparators for lanreotide been included in the scope? Which treatments are considered to be established clinical practice in the NHS for gastroenteropancreatic neuroendocrine tumours without disease progression?

- Is lutetium-177 DOTATATE used for treating gastroenteropancreatic neuroendocrine tumours without disease progression and should it be included in the scope as a comparator for lanreotide?

Are the subgroups suggested in other considerations appropriate? Are there any other subgroups of people in whom lanreotide is expected to be more clinically effective and cost effective or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which lanreotide is licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider

population, e.g. by making it more difficult in practice for a specific group to access lanreotide;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.