NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Everolimus, lanreotide, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression

Draft scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of everolimus, lanreotide, lutetium-177 DOTATATE and sunitinib within their marketing authorisation for treating unresectable or metastatic neuroendocrine tumours with 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), the lung (neuroendocrine cells within the respiratory epithelium) and thyroid. Depending on the data source used, approximately 45-65 % of neuroendocrine tumours occur in the gastrointestinal tissue, approximately 3-7 % in the pancreas and 10% in the lungs. 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, 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.

Neuroendocrine tumours of the lung are classified according to their histology and clinical outcome into typical carcinoid lung tumour and atypical carcinoid lung tumour. Typical carcinoid lung tumours grow slowly and rarely spread beyond the lungs. Atypical carcinoid lung tumours grow faster than typical tumours and are more likely to spread to other organs. Most neuroendocrine tumours of the lung are non-functioning and common symptoms are those associated with bronchial obstruction, such as persistent cough, coughing up blood, and recurrent or obstructive pneumonitis.

Surgery is the only curative treatment for neuroendocrine tumours. 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. Options for treating neuroendocrine tumours that have progressed include somastatin analogues, radionuclides, chemotherapy regimens (using combinations of streptozocin, 5-fluorouracil, doxorubicin, temozolomide and capecitabine), everolimus and sunitinib. Sunitinib is available on the cancer drugs fund.

This technology appraisal only considers lutetium-177 DOTATATE and lanreotide for the treatment of unresectable, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours with disease progression. Lutetium-177 DOTATATE and lanreotide for the treatment of unresectable, somatostatin receptor-positive gastroenteropancreatic neuroendocrine

tumours without disease progression is outside the scope of this appraisal and are subject to ongoing NICE appraisal (ID857 and ID961).

The technologies

Everolimus (Afinitor, Novartis), is an oral inhibitor of the mammalian target of rapamycin (mTOR) protein, a central regulator of tumour cell division and blood vessel growth in cancer cells. It has a marketing authorisation in the UK for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease. It does not currently have a marketing authorisation in the UK for the treatment of advanced neuroendocrine tumours of gastrointestinal or lung origin. It has been studied in clinical trials compared with placebo in adults with advanced unresectable or metastatic neuroendocrine tumours of gastrointestinal or lung origin.

Lanreotide (Somatuline Autogel, Ipsen) is an inhibitor of various endocrine, neuroendocrine, exocrine and paracrine functions. It is an analogue of natural somatostatin which binds to human somatostatin receptors (SSTR) which are present in the majority (75-95%) of neuroendocrine tumours. Lanreotide is administered by deep sub-cutaneous injection. It 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 or pancreatic or unknown origin where hindgut sites of origin have been excluded in adult patients with unresectable locally advanced or metastatic disease. The exact mechanism of action of lanreotide in delaying progression of gastroenteropancreatic neuroendocrine tumours is not known.

Lutetium-177 DOTATATE (Lutathera, Imaging Equipment) is a radio-labelled analogue of somatostatin. It kills tumour cells by binding to a specific type of somatostatin receptor, called sst2 receptors, which are overexpressed by the malignant cells. It does not currently have marketing authorisation in the UK for any indication. It has been studied in a clinical trial in people with inoperable, locally advanced or metastatic somastostatin receptor positive midgut neuroendocrine tumours (Ki67 index ≤ 20%) with or without disease progression compared with octreotide long acting release (LAR). It has also been studied in a single arm study in people with gastrointestinal or pancreatic neuroendocrine tumours with or without disease progression. Lutetium-177 DOTATATE is administered by intravenous infusion.

Sunitinib (Sutent, Pfizer) is a protein kinase inhibitor that works by preventing tumour proliferation and inhibiting blood vessel growth, leading to cancer cell death. It has a marketing authorisation for treating unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults. Sunitinib is administered orally.

Intervention(s)	• Everolimus (neuroendocrine tumours of gastrointestinal, pancreatic or lung origin) • Lanreotide (neuroendocrine tumours of mid-gut, pancreatic or unknown origin) • Lutetium-177 DOTATATE (neuroendeocrine tumours of gastrointestinal or pancreatic origin) • Sunitinib (pancreatic neuroendocrine tumours)
Population(s)	People with unresectable or metastatic neuroendocrine tumours and whose disease has progressed.
Comparators	• the technologies listed above will be compared with each other where appropriate. • chemotherapy regimens (including but not restricted to combinations of streptozocin, 5-FU, doxorubicin, temozolomide, capecitabine) • best supportive care
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

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. The use of lutetium-177 DOTATATE is conditional on the presence of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours. The economic modelling should include the costs associated with diagnostic testing for somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours in people who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the 'Guide to the Methods of Technology Appraisals'
Other considerations	If the evidence allows the following subgroups will be considered: • location of tumour • grade/degree of differentiation • stage of tumour • secretory profile • number of previous treatment(s) Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations and NICE Pathways	Appraisals in development: 'Lanreotide for treating unresectable locally advanced or metastatic gastroenteropancreatic neuroendocrine tumours without disease progression' [ID 961]. Anticipated publication date January 2017 Lutetium-177 DOTATATE for treating inoperable, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours without disease progression'. [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 the relevant comparators been included in the scope? In particular

- Should the following be included as comparators?
  - Interferon alpha?
  - Ablation therapy?
  - Radiotherapy?
  - Octreotide long acting release formulation?
- Which treatments are considered to be established clinical practice in the NHS for treating neuroendocrine tumours of lung origin?
- How should best supportive care be defined?

The use of lutetium-177 DOTATATE is conditional on the presence of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours. Is the diagnostic testing for somatostatin receptor-positive neuroendocrine tumours considered to be established clinical practice in the NHS?

Are the subgroups suggested in ‘other considerations appropriate? Are there any other subgroups of people in whom the technologies are 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 scope may need changing in order to meet these aims. In particular, please tell us if the scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the technologies are or will be 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 the technologies,

- 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.