NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Lutetium-177 for treating unresectable, somatostatin receptor-positive gastroentero-pancreatic neuroendocrine tumours

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of lutetium-177 within its marketing authorisation for treating unresectable, somatostatin receptor-positive gastroentero-pancreatic neuroendocrine tumours.

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. Approximately 85% of neuroendocrine tumours occur in the gastroenteric tissue and 3% 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 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 duodenum), midgut (jejunum, ileum, appendix, right colon) and hindgut (left colon, rectum). The incidence of neuroendocrine tumours of the gastrointestinal tissue in England 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 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 approximately 0.2-0.4 per 100,000 of the population per year. The incidence of pancreatic neuroendocrine tumours is age-related. Functioning tumours constitute approximately 60% of all pancreatic neuroendocrine tumours, with insulinoma (produces too much insulin) and glucagonoma (produces too much glucagon) 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 non-specific symptoms such as bowel obstruction.

Surgery is the only curative treatment for gastroentero-pancreatic neuroendocrine tumours. For people who are unable to have surgery, the choice of treatment depends on the symptoms, stage of disease, and histological features of the tumour. Somatostatin analogues such as octreotide and lanreotide are used to relieve symptoms caused by the tumour. Options for treating the tumour after somatostatin analogues, especially following disease progression, include chemotherapy regimens (using combinations of lomustine, dacarbazine, 5-fluorouracil and doxorubicin), everolimus and sunitinib. Sunitinib is currently available on the cancer drugs fund for treating well- or moderately-differentiated neuroendocrine tumours of pancreatic origin with progressive disease.

The technology

Lutetium-177 (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. Lutetium-177 is administered by intravenous infusion.

Lutetium-177 does not currently have marketing authorisation in the UK for any indication. It has been studied in clinical trials compared with octreotide or interferon alpha-2b in adults with inoperable, somastatin-receptor positive neurondeocrine tumours of gastro-intestinal or pancreatic origin. It has also been studied in people with somatostatin-analogue resistant gastro-neuroendocrine tumours.

Intervention(s)	Lutetium-177
Population(s)	Adults with unresectable, somastatin receptor-positive gastroentero-pancreatic neuroendocrine tumours without disease progression

Comparators	For gastroentero neuroendocrine tumours: • octreotide (long-acting release formulation) • lanreotide (subject to proposed NICE appraisal) For pancreatic neuroendocrine tumours: • lanreotide (subject to proposed NICE appraisal) • best supportive care • watchful waiting
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. Where comparator technologies are available through the Cancer Drug Fund, the cost incurred by the Cancer Drug Fund should be used in any economic analyses, rather than the list price.

Other considerations	If the evidence allows the following subgroups will be considered: • location of tumour • tumour size • degree of differentiation • stage of tumour • secretory profile Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Proposed appraisal 'Lanreotide for treating advanced or metastatic, unresectable gastroentero-pancreatic neuroendocrine tumours without disease progression'. Proposed NICE technology appraisal. ID858. Publication date to be confirmed. Proposed appraisal 'Everolimus, lanreotide and sunitinib for treating unresectable or metastatic gastroentero-pancreatic neuroendocrine tumours with progressed disease'. Proposed NICE technology appraisal. 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

Questions for consultation

Should the scope only consider the use of lutetium-177 in people with gastroentero pancreatic neuroendocrine tumours without disease progression?

Have all relevant comparators been included in the scope? In particular:

- Which treatments are considered to be established clinical practice in the NHS in England for treating unresectable somatostatin receptor-positive gastroentero-pancreatic tumours without disease progression?
- Does treatment vary depending on the origin of the tumour?
- How should best supportive care be defined?

Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom lutetium-177 are expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider lutetium-177 will fit into the existing NICE pathway, 'Metastatic malignant disease of unknown primary origin overview'?

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 lutetium-177 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 technology;

- 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.

Do you consider lutetium-177 to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of lutetium-177 can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

It is proposed that NICE will consider this technology for tumours without disease progression through the single technology appraisal (STA) process. A multiple technology appraisal (MTA) for 'Everolimus, lanreotide and sunitinib for treating advanced or metastatic unresectable gastroentero-pancreatic neuroendocrine tumours with progressed disease' is currently being considered. Should lutetium-177 also be included in this MTA for progressed disease, (in addition to considering use in tumours without disease progression in the STA), or do you consider that it would be more appropriate to consider this technology for progressed and non-progressed disease together through an MTA? We welcome comments on the appropriateness of appraising this topic through either process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

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