NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Lutetium-177 DOTATATE for treating unresectable, somatostatin receptor-positive non-progressive gastroenteropancreatic neuroendocrine tumours

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of lutetium-177 DOTATATE within its marketing authorisation for treating unresectable, somatostatin receptor-positive 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, 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 non-progressive tumours. 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 lutetium-177 DOTATATE for the treatment of unresectable, somatostatin receptor-positive non-progressive gastroenteropancreatic neuroendocrine tumours. Lutetium-177 DOTATATE for the treatment of unresectable, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours with disease progression is outside the scope of this appraisal and is subject to another ongoing NICE appraisal (ID858).

The technology

Lutetium-177 DOTATATE (Lutathera, Advanced Accelerator Applications) is a radio-labelled analogue of somatostatin designed to deliver radiation to cells. 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 DOTATATE is administered by intravenous infusion.

Lutetium-177 DOTATATE does not currently have a 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.

Intervention(s)	Lutetium-177 DOTATATE
Population(s)	Adults with unresectable, somastatin receptor-positive gastroenteropancreatic neuroendocrine tumours **and** • have non-progressive disease [1]
Comparators	For gastrointestinal neuroendocrine tumours: • octreotide (long-acting release formulation) • lanreotide For pancreatic neuroendocrine tumours: • lanreotide • 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

[1] Lutetium-177 DOTATATE for the treatment of unresectable, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours 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. 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: • stage of tumour • location of tumour • secretory profile Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations and NICE Pathways	Appraisals in development: 'Lanreotide for treating advanced or metastatic, unresectable gastroentero-pancreatic neuroendocrine tumours without disease progression'. [ID961]. Anticipated date of publication TBC. 'Everolimus, lutetium-177 and sunitinib for treating unresectable or metastatic neuroendocrine tumours with progressed disease'. [ID858], Anticipated date of publication August 2017. 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

References

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