NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Everolimus, lanreotide and sunitinib for treating advanced or metastatic, unresectable gastroentero-pancreatic tumours

Draft scope (pre-referral)

Draft remit/appraisal objective
To appraise the clinical and cost effectiveness of everolimus, lanreotide and sunitinib within their marketing authorisation for treating advanced or metastatic, unresectable gastroentero-pancreatic 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%.

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. 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 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 include interferon alfa, radionuclides, ablation therapies, chemotherapy regimens (using combinations of lomustine, dacarbazine, 5-fluorouracil and doxorubicin), everolimus and sunitinib. Both everolimus and sunitinib are available on the cancer drugs fund for treating well- or moderately-differentiated neuroendocrine tumours of pancreatic origin with progressive disease.

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 for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.

Lanreotide (Somatuline Autogel and Somatuline LA, 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 sub-cutaneous injection.

Lanreotide (Somatuline Autogel) has a marketing authorisation in the UK for treating Grade 1 and a subset of Grade 2 (Ki67 index up to 10%) gastroentero-pancreatic neuroendocrine tumours (GEP-NETs) of mid-gut or pancreatic origin in adult patients with unresectable locally advanced or metastatic disease.

Lanreotide (Somatuline Autogel, Somatuline LA) has a marketing authorisation in the UK for the treatment of individuals with the symptoms associated with neuroendocrine (particularly carcinoid) tumours (NETs) and for the relief of symptoms associated with neuroendocrine (particularly carcinoid) tumours respectively.
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.

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<tr>
<th>Intervention(s)</th>
<th>Everolimus (pancreatic neuroendocrine tumours only)</th>
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<tr>
<td></td>
<td>Lanreotide (gastroentero-pancreatic tumours)</td>
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<td>Sunitinib (pancreatic neuroendocrine tumours only)</td>
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| Population(s)                            | Adults with locally advanced or metastatic unresectable neuroendocrine tumours of gastro-intestinal or pancreatic origin |

<table>
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<tr>
<th>Comparators</th>
<th>the technologies listed above will be compared with each other.</th>
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<tr>
<td></td>
<td>octreotide (long-acting release formulation)</td>
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<td>interferon alfa</td>
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<td>chemotherapy regimens using combinations of lomustine, dacarbazine, 5-fluorouracil and doxorubicin</td>
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<tr>
<th>Outcomes</th>
<th>The outcome measures to be considered include:</th>
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<td>health-related quality of life</td>
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### 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.

### Related NICE recommendations and NICE Pathways

Related Technology Appraisals:

Proposed appraisal ‘lutetium-177 for treating inoperable, somatostatin receptor-positive gastroentero-pancreatic neuroendocrine tumours’ Proposed NICE technology appraisal. 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


### Related National Policy

NHS England commissions adult specialist endocrine services from Adult Specialist Endocrinology Centres for specified condition, including the management of neuro-
Questions for consultation

Should both functioning and non-functioning gastroentero-pancreatic tumours be considered in the scope?

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 advanced or metastatic unresectable gastroentero-pancreatic tumours?
- Does treatment vary depending on the origin of the tumour?
- Is interferon alfa considered established clinical practice in the NHS in England?
- Where does radiotherapy fit into the clinical pathway?
- How should best supportive care be defined?

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

Where do you consider everolimus, lanreotide and sunitinib 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 everolimus, lanreotide and sunitinib are 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 everolimus, lanreotide and sunitinib to be innovative in their 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 everolimus, lanreotide or sunitinib 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.

NICE intends to appraise this technology through its Multiple Technology Appraisal (MTA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute’s Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)

References