NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of regorafenib within its marketing authorisation for unresectable or metastatic gastrointestinal stromal tumours in people whose disease progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib.

Background

Gastrointestinal stromal tumours (GISTs) are rare connective tissue tumours. Although GISTs can occur along the length of the gastrointenstinal (GI) tract, the majority arise in the stomach (60–70%) or small intestine (25–35%)[1]. GISTs are associated with overexpression of several tyrosine kinase growth receptors. Around 75–80% of GISTs have activating mutations in the c-KIT receptor (a tyrosine kinase receptor) and 5–10% in platelet-derived growth factor receptors [2]. These mutations are thought to affect tumour development.

There are approximately 900 new diagnoses of GIST per year in the UK and approximately half of these are likely to be resectable [3]. Although GISTs can occur at any age, the median age at presentation is 55-65 years and is more common in men than women [4].

Complete surgical excision is the current standard treatment for localised GISTs. The risk of recurrence after surgery varies by a number of factors including the size and anatomical location of the primary GIST. Disease can be classified by risk. A study on resected metastatic-only GIST patients demonstrated median survival was 19 months with a 41% 2-year survival and a 25% 5-year survival [5].

NICE technology appraisal 86 recommends imatinib for first-line treatment for people with c-Kit-positive unresectable and/or metastatic GISTs. However, it is not recommend for people with unresectable and/or metastatic GISTs whose disease has progressed after previous treatment with imatinib. NICE technology appraisal guidance 179 recommends sunitinib as a second-line treatment option after failure of imatinib because of resistance or intolerance. Regoragenib has been available on the Cancer Drugs Fund for the treatment of ‘patients with advanced (metastatic or unresectable) gastrointestinal stromal tumours after failure of at least previous imatinib and sunitinib’.

The technology

Regorafenib (Stivarga, Bayer) inhibits angiogenic kinase receptors, such as the vascular endothelial growth factor and the TIE2 receptor, which play a role in angiogenesis. It also inhibits oncogenic kinases such as RAF, RET and cKIT, thereby preventing the proliferation of cancer cells. It is administered orally.

Regorafenib has a marketing authorisation in the UK for 'unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib'.

Intervention(s)	Regorafenib
Population(s)	People with unresectable or metastatic gastrointestinal stromal tumours whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib
Comparators	Best supportive care
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • 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.
Other considerations	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 appraisal guidance: 'Imatinib for the adjuvant treatment of gastrointestinal stromal tumours' (2014). NICE Technology appraisal

	326. Review date: 2017 'Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours' (2010). NICE Technology appraisal 209 part review of NICE technology appraisal guidance 86' 'Sunitinib for the treatment of gastrointestinal stromal tumours' (2009). NICE Technology appraisal 179. Guidance on static list 'Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours' (2004) NICE Technology appraisal 86. This guidance has been partially updated by 'Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours' (NICE technology appraisal guidance 209) Related Cancer Service Guidance: Cancer Service Guidance, March 2006 'Improving outcomes for people with sarcoma' Cancer Service Guidance, March 2004 'Improving supportive and palliative care for adults with cancer' Related Quality Standards: Quality Standard 'End of life care for adults' Related NICE Pathways: Nice Pathway: Gastrointestinal cancers. Pathway created: Feb 2016. http://pathways.nice.org.uk/pathways/gastrointestinal-cancers
Related National Policy	Manual for prescribing specialised services 2016/17 105. Specialist cancer services (adults): https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf The national cancer strategy: 4th annual report:https://www.gov.uk/government/publications/the-national-cancer-strategy-4th-annual-report Department of Health, NHS Outcomes Framework 2016-17, April 2016 . Domains 1, 2, 4 and 5:https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for regorafenib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for people who have been previously treated with imatinib and sunitinib for GIST?

- How is best supportive care defined in people who progressed on or are intolerant to prior treatment with imatinib and sunitinib?

- Are the outcomes listed appropriate?

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

Where do you consider regorafenib will fit into the existing NICE pathway, gastrointestinal cancers?

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 regorafenib 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 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 regorafenib 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 regorafenib 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 Single Technology Appraisal (STA) 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

1 Jakhetiya A, Garg PK, Prakash G, Sharma J, Pandey R, Pandey D. Targeted therapy of gastrointestinal stromal tumours. World J Gastrointest Surg 2016; 8(5): 345-352

2 Braconi C, Bracci R, Cellerino R Molecular targets in Gastrointestinal Stromal Tumors (GIST) therapy. Curr Cancer Drug Targets. 2008 Aug;8(5):359-66.

3. Kindblom LG, "Gastrointestinal Stromal Tumors Diagnosis, Epidemiology and Prognosis" in "Gastrointestinal Stromal Tumors: Current management and Future Challenges". Chair: Blanke CD. ASCO 2003

4. Kong S-H, Yang H-K. Surgical Treatment of Gastric Gastrointestinal Stromal Tumor. Journal of Gastric Cancer. 2013;13(1):3-18. doi:10.5230/jgc.2013.13.1.3.

5. Gold, J.S., van der Zwan, S.M., Gönen, M. et al. Outcome of Metastatic GIST in the Era before Tyrosine Kinase InhibitorsAnn Surg Oncol (2007) 14: 134. doi:10.1245/s10434-006-9177-7