National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours ID1056

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Sarcoma UK	Yes	Thank you for your comment
	Bayer Plc	No comment	
	GIST Support UK	Yes	Thank you for your comment
Timing Issues	Sarcoma UK	No comment	
	Bayer Plc	Currently, patients with unresectable or metastatic gastrointestinal stromal tumours (GISTs) whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib have no other treatment option other than best supportive care. Regorafenib will be the only licensed treatment available for these patients.	Comment noted

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	GIST Support UK	Urgent Currently GIST patients who are intolerant of Imatinib and Sunitinib or whose disease progresses on these drugs access Regorafenib via the Cancer drug fund. Without Regorafenib their only available option is best supportive care.	Comment noted
Additional comments on the draft remit	Sarcoma UK	No comment	
	Bayer Plc	No comment	
	GIST Support UK	No comment	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Sarcoma UK	Accurate	Thank you for your comment
	Bayer Plc	None	
	GIST Support UK	The background information is accurate. Regorafenib is for all types of GIST cancer patients including those who have no detectable mutations in the KIT or PDGFRA genes in their tumours and those who have metastatic disease at diagnosis, may have had surgery but are not free of the disease.	Comment noted

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The technology/ intervention	Sarcoma UK	Accurate but incomplete. The crucial importance of regorafenib is its ability to inhibit certain secondary acquired mutations in the KIT gene that confer resistance to imatinib and sunitinib	Comment noted. The background section is intended to be a short summary of the disease area.
	Bayer Plc	Yes	Thank you for your comment
	GIST Support UK	The description is accurate but missing the fact that regorafenib inhibits secondary mutations that occur when a GIST patient's tumour becomes resistant to imatinib and sunitinib.	Comment noted. The background section is intended to be a short summary of the disease area.
Population	Sarcoma UK	There is one population that has not been considered, which is the group of patients with no detectable mutations in the KIT or PDGFRA genes in their tumour for whom imatinib is largely ineffective. This is so-called "wild-type" disease. Sunitinib has some activity and regorafenib has also been reported to be active.	Comment noted. Regorafenib will be appraised within its marketing authorisation for people with unresectable or metastatic gastrointestinal stromal tumours whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib.

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	Bayer Plc	The population is defined appropriately	Thank you for your comment
	GIST Support UK	The population defined includes all types of GIST cancer patients. We do not think that there are groups that should be considered separately.	Comment noted
Comparators	Sarcoma UK	Yes, best alternative care would include other agents, novel tyrosine kinase inhibitors (TKIs) and drugs directed against other targets, in clinical trial, and sometimes reintroduction of imatinib for symptom control and symptomatic measures. The use of imatinib in this situation is not currently recommended by NICE, but symptom flare on stopping all TKIs is a very real phenomenon that is seen in other diseases such as renal cancer. A study performed in South Korea showed limited duration of objective benefit, but maintained quality of life(1, 2). Short term benefit in symptom control is valuable to patients.	Comment noted. NICE defines comparators on the basis of clinical practice and can not therefore consider experimental treatments.
	Bayer Plc	No other treatments are licensed for this indication. Best supportive care is the appropriate comparator for this appraisal	Thank you for your comment
	GIST Support UK	Best supportive care is currently the only comparator available in the absence of Regorafenib. Regorafenib is the only third line drug available to GIST patients whose disease has progressed on Imatinib and Sunitinib. Regorafenib is what stands between GIST patients and death.	Comment noted
Outcomes	Sarcoma UK	Yes, note that a study of health utility in patients being treated in the GRID phase III randomised clinical trial has been published and would be useful for reference(3).	Comment noted
	Bayer Plc	Yes	Thank you for your comment
	GIST Support UK	Yes	Thank you for your comment

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Economic analysis	Sarcoma UK	Provided regorafenib continues to be available via the Cancer Drug Fund this is acceptable.	Comment noted. The process for the appraising drugs which are currently available on the CDF can be found on the NICE website (https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund).
	Bayer Plc	Appropriate time horizon	Thank you for your comment
	GIST Support UK	Economic analysis will not factor in the benefit to GIST cancer patients and society in general that this drug affords, such as: Hope – disease management, a future… Time – to find improved treatments Life – to be lived to the full. Regorafenib is:: Well tolerated – with dose management Improves PFS Is easy to take Reduces psychological distress Enables a normal lifestyle and continuation of a working life or studies.	Comment noted. In accordance with section 4.3 of the methods guide, we invite submissions from patient and carer groups and they can describe their perspectives on the disease and highlight for the committee's consideration any

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		Most of these aspects are unlikely to be included in economic analysis.	health benefits that may not be captured in the economic analysis. https://www.nice.org.uk/process/pmg9/chapter/involvement-and-participation#patient-and-carer-groups.
Equality and Diversity	Sarcoma UK	One issue is the group with wild-type disease and the possibility that treatment with regorafenib might be considered appropriate earlier in the course of the disease because of the inactivity of imatinib. Another key issue, which will become increasingly relevant as the technology improves, is those patients with acquired resistance due to mutations in exon 17 of KIT who will not respond to sunitinib but are likely to respond to regorafenib. It is likely to become routine within the next few years to test for resistant mutations in the blood by sequencing circulating tumour DNA (ctDNA)(4). If this information is available it would be logical, indeed both ethically appropriate and financially astute, to treat a patient with acquired KIT exon 17 mutation using regorafenib rather than having to give sunitinib and demonstrate disease progression first, which would be ineffective, costly, harmful and likely to result in poorer survival.	Comment noted. However in line with defined processes Regorafenib can only be appraised within the scope of its marketing authorisation, that is in people with unresectable or metastatic gastrointestinal stromal tumours whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib.
	Bayer Plc	No comment	
	GIST Support UK	We are very keen to ensure that Regorafenib remains available to GIST patients in England and given its proper status as the NICE approved third line drug for GIST patients. Regorafenib has been rigorously reviewed and is	Comment noted

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		now fully approved as the third line treatment for GIST patients both in Scotland and Wales.	
Other considerations	Sarcoma UK	The main issue is activity against secondary mutations that confer resistance to sunitinib (5-7)	Comment noted
	Bayer Plc	None	
	GIST Support UK	The appraisal needs to ensure inclusion of regorafenib and its use in GIST patients whose disease progresses on or who are intolerant to Imatinib and Sunitinib and also those who acquire secondary mutations that are resistant to other treatments.	Comment noted
Innovation	Sarcoma UK	Yes, it is a significant step forward in relation to the ability to treat certain patients with acquired resistance to imatinib and sunitinib.	Thank you for your comment
	Bayer Plc	Currently, best supportive care is the only treatment option for patients with unresectable or metastatic GISTs whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib. Regorafenib therefore represents a step-change in the management of the condition	Comment noted
	GIST Support UK	This technology is not only innovative, it is making a substantial impact for patients and their treating clinicians. It represents a huge “step change” in the way that GIST is managed. c.40% of GIST patients have advanced disease at diagnosis. These 40% often find that: * Imatinib does not work * they are not able to tolerate sunitinib *Regorafenib is the first drug that stabilises their disease and is well tolerated. All sunitinib users are comforted by the fact that regorafenib is an option when their disease progresses. Patients already using regorafenib are experiencing clinical benefit and in some cases tumour shrinkage where this has not happened previously.	Comment noted. The company and other consultees will be able to fully describe why they consider regorafenib to be innovative in their evidence submissions, which will then be considered by the appraisal committee.

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		Regorafenib benefits patients by giving: Hope – disease management, a future… Time – to find improved treatments Life – to be lived to the full. Regorafenib benefits patients by: Being well tolerated – with dose management Improving PFS Being easy to take Reducing psychological distress Enabling a normal lifestyle Most of these aspects are unlikely to be included in the QALY calculation. As the UK's only charity focused solely on the support of GIST cancer patients we canprovide real live case studies from patients who are benefitting from access to regorafenib as their third line treatment for GIST cancer and the impact this has had on their lives.	
Questions for consultation	Sarcoma UK	A single technology appraisal process would seem to be appropriate, since there are no other licensed agents currently available for the treatment of GIST after failure of imatinib and sunitinib.	Thank you for your comment
	Bayer Plc	No comment	
	GIST Support UK	It is appropriate to use a single technology appraisal as there are no other drugs available to GIST patients when imatinib and sunitinib have failed.	Thank you for your comment
Additional comments on the draft scope	Sarcoma UK	GIST is a type of soft tissue sarcoma. Therefore, this section should include the Sarcoma Quality Standard (QS 78), Jan 2015; and the Sarcoma Pathway https://pathways.nice.org.uk/pathways/sarcoma The Pathway for Gastrointestinal cancers cited in the draft scope does not cover GIST. References	Thank you for your comment. The pathway has been amended to http://pathways.nice.org.uk/pathways/gastrointestinal-

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		There are a number of additional references that should inform this draft scope. 1. Kang YK, Ryu MH, Yoo C, Ryoo BY, Kim HJ, Lee JJ, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. The lancet oncology. 2013;14(12):1175-82. 2. Yoo C, Ryu MH, Nam BH, Ryoo BY, Demetri GD, Kang YK. Impact of imatinib rechallenge on health-related quality of life in patients with TKI-refractory gastrointestinal stromal tumours: Sub-analysis of the placebo-controlled, randomised phase III trial (RIGHT). Eur J Cancer. 2016;52:201-8. 3. Poole CD, Connolly MP, Chang J, Currie CJ. Health utility of patients with advanced gastrointestinal stromal tumors (GIST) after failure of imatinib and sunitinib: findings from GRID, a randomized, double-blind, placebo-controlled phase III study of regorafenib versus placebo. Gastric Cancer. 2015;18(3):627-34. 4. Kang G, Bae BN, Sohn BS, Pyo JS, Kang GH, Kim KM. Detection of KIT and PDGFRA mutations in the plasma of patients with gastrointestinal stromal tumor. Target Oncol. 2015;10(4):597-601. 5. Heinrich MC, Maki RG, Corless CL, Antonescu CR, Harlow A, Griffith D, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol. 2008;26(33):5352-9. 6. Heinrich MC, Marino-Enriquez A, Presnell A, Donsky RS, Griffith DJ, McKinley A, et al. Sorafenib inhibits many kinase mutations associated with drug-resistant gastrointestinal stromal tumors. Mol Cancer Ther. 2012;11(8):1770-80. 7. Van Looy T, Gebreyohannes YK, Wozniak A, Cornillie J, Wellens J, Li H, et al. Characterization and assessment of the sensitivity and resistance of a newly established human gastrointestinal stromal tumour xenograft model	cancers/stomach#content=view-node:nodes-gastrointestinal-stromal-tumours

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		to treatment with tyrosine kinase inhibitors. Clinical sarcoma research. 2014;4:10.	
	Bayer Plc	None	
	GIST Support UK	Should the National GIST Guidelines be referenced in the draft scope?	Comment noted. The scope is intended to be a short summary of the disease area. Stakeholders are encouraged to refer to any relevant guidelines which inform the treatment pathway within their evidence submission to NICE.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health