National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Regorafenib for the treatment of metastatic colorectal cancer following prior treatment for metastatic disease

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

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Bayer plc	Bayer does not feel that it is appropriate to refer this topic for NICE appraisal. The EU indication for regorafenib is likely to be for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. This is in line with the US indication recently approved by the FDA. Under current NICE guidelines, this population does not exist in England & Wales. The pivotal study, CORRECT, on which the licence application for regorafenib is based, required that patients had to have previously received bevacizumab and, if KRAS wild-type, cetuximab or panitumumab to be enrolled. These are recognised standard treatments internationally and recommended by all major US and EU treatment guidelines. Contrary to the international treatment guidelines, NICE do not recommend the use of bevacizumab, cetuximab or panitumumab in England & Wales for mCRC (TA242, January 2012). As these treatments are not standard practice in the UK, it was not possible to include any UK patients into the trial. There isn't at this time, an evidence base on which to compare regorafenib in	Thank you for your comment. The decision to refer a topic for NICE appraisal is made at the Ministers' discretion, and takes account of the comments received during the draft scope consultation and the discussion that took place at the scoping workshop. Attendees at the scoping workshop indicated that patients in England receive bevacizumab and cetuximab through

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Appropriateness (cont.)	Bayer plc (cont.)	metastatic colorectal cancer against standard UK practice There is use of bevacizumab and cetuximab or panitumumab within the CDF however our understanding is that products used in the CDF should not be considered comparators since they are not necessarily cost effective and the CDF is not available in Wales. Based on the above considerations, we feel that assessing regorafenib with currently available data would not be a useful use of resources at this time and would not add value for the NHS.	the Cancer Drugs Fund, and therefore would be eligible for treatment with regorafenib under the anticipated marketing authorisation. The relevance of the available evidence in relation to UK clinical practice would be considered by the Committee during the course of the appraisal. No action required.
Wording	Bayer plc	No, the remit would be to appraise regorafenib within its licensed indication for the treatment of metastatic colorectal cancer that has progressed following the use of therapies which must include fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if KRAS WT). As bevacizumab, cetuximab and panitumumab are not recommended by NICE for use within standard clinical practice in England and Wales, an appraisal does not seem feasible based on the current NICE guidance and the resultant lack of evidence base.	Thank you for your comment. Attendees at the scoping workshop agreed to keep the remit broad to allow for any uncertainty around the final marketing authorisation. No action required.

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Timing Issues	Bayer plc	Regorafenib will not be considered for use under the NHS in England and Wales as its use is precluded by current NICE guidance on treatments which should be used earlier in the treatment pathway. As such, there would appear to be no urgency in its appraisal. There is an additional trial ongoing in Asia Pacific which will compare regorafenib against pathway of care currently used in England and Wales. This trial is expected to complete in May 2014. At this time we would expect regorafenib to be of relevance to recommended standards of care in England and Wales and believe an appraisal at this time would add value of the NHS.	Thank you for your comment. Attendees at the scoping workshop indicated that patients in England receive bevacizumab and cetuximab through the Cancer Drugs Fund, and therefore would be eligible for treatment with regorafenib under the anticipated marketing authorisation. No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Bayer plc	Bayer has no comments	No action required.
The technology/ intervention	Bayer plc	The second paragraph states that "it has been studied in clinical trials compared with placebo for the treatment of metastatic colorectal cancer whose disease has progressed after standard therapies". As already stated, the standard therapies specified in the Phase III trial protocol are not part of recommended clinical practice in England and Wales and this should be acknowledged. As such, there isn't an evidence base on which to compare regorafenib in metastatic colorectal cancer against standard practice in England and Wales.	Thank you for your comment. The technology section of the scope includes information about the pivotal clinical trials to give a general scope of the key sources of evidence irrespective of current clinical practice. The relevance of the available evidence in relation to UK clinical practice would be considered by the Committee during the course of the appraisal. No action required.

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Population	Bayer plc	As stated the population does not exist in England and Wales.	Thank you for your comment. Attendees at the scoping workshop indicated that patients in England receive bevacizumab and cetuximab through the Cancer Drugs Fund, and therefore would be eligible for treatment with regorafenib under the anticipated marketing authorisation. No action required.

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Questions for consultation	Bayer plc	***Given the available interventions and current clinical practice in the NHS, what is the likely place of regorafenib in the treatment pathway for metastatic colorectal cancer?*** Bayer does not anticipate use in the NHS except under exceptional circumstances. We would expect that use will mainly be in the private market. ***The comparator in the scope assumes that the place of regorafenib is subsequent to all prior treatments. Is best supportive care therefore the most appropriate comparator for regorafenib for the treatment of metastatic colorectal cancer? Are there other comparators that would be considered in routine clinical practice at the stage in therapy at which regorafenib is likely to be used?*** See above ***How should best supportive care be defined?*** ***Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?***	Thank you for your comment. Attendees at the scoping workshop indicated that patients in England receive bevacizumab and cetuximab through the Cancer Drugs Fund, and therefore would be eligible for treatment with regorafenib under the anticipated marketing authorisation. The relevance of the available evidence in relation to UK clinical practice would be considered by the Committee during the course of the appraisal. No action required.

Section	Consultees	Comments	Action
Questions for consultation (cont.)	NCRI/RCP/ RCP/ACP/ JCCO	• *Given the available interventions and current clinical practice in the NHS, what is the likely place of regorafenib in the treatment pathway for metastatic colorectal cancer?* *Would be used in third line setting for patients who have received prior active agents and progressed. For those patients who are KRAS wt, cetuximab may be used third line and regorafenib would be used 4th line.* • *The comparator in the scope assumes that the place of regorafenib is subsequent to all prior treatments. Is best supportive care therefore the most appropriate comparator for regorafenib for the treatment of metastatic colorectal cancer? Are there other comparators that would be considered in routine clinical practice at the stage in therapy at which regorafenib is likely to be used?"* *Palliative care would be the most appropriate comparator.* • Are there patients in the NHS who receive bevacizumab, cetuximab or panitumumab for mCRC (possibly through the Cancer Drugs Fund)? As the anticipated marketing authorisation is likely to limit the use of regorafenib to those patients. In England patients routinely receive bevacizumab and cetuximab through the CDF and would thus be eligible for regorafenib under the Marketing Authorisation.	Thank you for your comment. The population in the scope covers patients who would be eligible for regorafenib as a third- or fourth-line treatment. Attendees at the scoping workshop agreed that both 'best supportive care' and 'palliative care' primarily aim to manage disease-related symptoms and therefore could be used interchangeably. No action required.

Section	Consultees	Comments	Action
Additional comments on the draft scope.	Dr Patrick Cadigan, RCP registrar submitting on behalf of: NCRI/RCP/RCR /ACP/JCCO	We are grateful for the opportunity to consider the draft scope. Overall, we are happy with the document and have no comments to make.	No action required.
	NCRI/RCP/ RCP/ACP/ JCCO (additional comments)	*"The most likely place of regorafenib in the treatment pathway for metastatic colorectal cancer is a third line treatment. The trend now is to use Bevacizumab together with XELOX or FOLFOX as first line. FOLFIRI and Cetuximab are more commonly being used as second line. There is no effective third line of treatment for mCRC, therefore using best supportive are as a comparator looks reasonable. Regorafininb has similar side effects to Bevacizumab. The only advantage I can see (at the moment) is the fact that it is given orally (more convenient to patients and save time and resources within the NHS). A subgroup of people whom this drug may have adverse impact on are the people who cannot swallow tablets for any reason."*	Thank you for your comment. The population in the scope covers patients who would be eligible for regorafenib as a third-line treatment. No action required.
	Royal College of Pathologists	I have read the draft scope and while this seems very interesting, I can't see any issues that immediately come to mind for pathology. In particular, I am not aware of a test that is available that would predict response to regorafenib - or anything else that pathology laboratories would have to do additional to current procedures, should this drug gain approval for use in this situation. I have not commented on the specific areas below.	Thank you for your comment. No action required.

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

Department of Health
Medicines and Healthcare products Regulatory Agency
NHS Tees
The Royal College of Nursing