National Institute for Health and Care Excellence

Health Technology Evaluation

Regorafenib for treating metastatic colorectal cancer

Response to consultee and commentator comments on the draft remit and draft scope

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 and proposed process

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Bayer	Appropriate	Thank you for your comment. No action needed.
Timing Issues	Bayer	Bayer requested the appraisal of regorafenib in this indication as we have been approached by clinicians asking us to make a submission to NICE. The clinicians see a need for an additional effective chemo-free treatment option in this population of patients who have a poor prognosis.	Thank you for your comment. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Bayer	The background information is focussed on treatments given at 1st and 2nd line i.e. FOLFOX, FOLFIRI, single agent irinotecan, raltitrexed. This background is not in keeping with regorafenib's marketing authorisation in which regorafenib is an option after these agents.	Thank you for your comment. The background section aims to provide a brief

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			summary of the disease and how it is managed. It is written to be consistent with relevant published NICE technology appraisals, where appropriate. The management of previously treated colorectal cancer is discussed. No change to the scope needed.
The technology/ intervention	Bayer	The description is accurate but would benefit from a little more detail. We would suggest using the wording on regorafenib's mechanism of action (provided in italics below) which is taken from the SmPC. *Regorafenib is an oral tumour deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAF ^{V600E}) metastasis (VEGFR3, PDGFR, FGFR) and tumour immunity (CSF1R).* The wording of the license is not complete. Please could the full wording be used i.e. *Regorafenib has a marketing authorisation in the UK for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies. These include*	Thank you for your comment. Scopes issued after the 1st February 2022 no longer describe the mechanism of action. The mechanism of action and mode of administration have been removed from the final scope. The wording of the marketing authorisation has been revised.

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		fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy.	
Population	Bayer	The population is defined appropriately.	Thank you for your comment. No action needed.
Comparators	Bayer	**Irinotecan, FOLFIRI, FOLFOX, raltitrexed** The inclusion of these first four comparators is in direct conflict with the remit of the appraisal which is to assess regorafenib **within** its marketing authorisation (in italics below). *Regorafenib is indicated as monotherapy for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy* The listed treatments were available before regorafenib was licensed in mCRC and fall under the definition of "available therapies" in the license wording. Consequently regorafenib is not an alternative to these agents and they are not comparators. The registration trials for regorafenib investigated its use in patients who had received these 'available therapies'. **Nivolumab with ipilimumab & Encorafenib plus cetuximab**	According to NICE's method guide, all potentially relevant comparators should be identified. Retreatment with Irinotecan, FOLFIRI, FOLFOX and raltitrexed is possible also still possible. This is in line with other scopes in this area or second line plus treatments. Best supportive care also remains a comparator. The comparators listed in the scope aims to be inclusive. A rationale should be provided for excluding any comparators from the evidence submission, which can be considered by the appraisal committee.

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		These regimens are used if genetic testing indicates 1) for nivolumab with ipilimumab - high microsatellite instability or mismatch repair deficiency 2) for encorafenib plus cetuximab – BRAF V600E mutation-positive If genetic testing is positive these agents provide targeted therapy and are the treatment of choice. Regorafenib would not be considered an alternative option in the presence of such positive genetic tests and is not a comparator to these regimens. **Trifluridine-tipiracil** Trifluridine-tipiracil has a near identical license to regorafenib and is recommended as a 3rd or later line therapy. As such it occupies the same position in the treatment pathway where regorafenib will be considered and is the key comparator (or "best alternative care" for this appraisal). Global guidelines (ESMO 2016 (1), ASCO 2020 (2)) position trifluridine-tipiracil and regorafenib alongside each other as options in the 3rd or later-line setting. **Best Supportive Care** Since regorafenib was licensed trifluridine-tipiracil has become available and provides a new last treatment line before BSC. Regorafenib is considered an alternative to trifluridine-tipiracil and not as an alternative to BSC. References	

Section	Consultee/ Commentator	Comments [sic]	Action
		1) Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016; 27(8):1386-422. 2) Chiorean EG, Nandakumar G, Fadelu T, et al. Treatment of Patients With Late-Stage Colorectal Cancer: ASCO Resource-Stratified Guideline. JCO Glob Oncol. 2020; 6:414-38	
	Pierre Fabre Ltd	The relevant comparators relevant to the position in regorafenib in the treatment pathway are: • FOLFIRI (after either FOLFOX or CAPOX) • FOLFOX (after either FOLFIRI or CAPOX) • Raltitrexed (if 5-FU/FA are not suitable) • Trifluridine–tipiracil • Best supportive care Nivolumab with ipilimumab and encorafenib plus cetuximab are not relevant comparators on the basis that they are used earlier in the treatment pathway than regorafenib and for specific groups of patients. In particular, encorafenib plus cetuximab is the only licensed targeted treatment specific to BRAF V600E and as per NICE TA668 is recommended for specifically treating BRAF V600E mutation-positive metastatic colorectal cancer in adults who have had previous systemic treatment.	According to NICE's method guide, all potentially relevant comparators should be identified.
Outcomes	Bayer	Yes	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Economic analysis	Bayer	No comment	Thank you for your comment. No action needed.
Equality and Diversity	Bayer	None	Thank you for your comment. No action needed.
Other considerations	Bayer	No comment	Thank you for your comment. No action needed.

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

Merck Serono Ltd
Servier Laboratories