National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Trifluridine in combination with tipiracil hydrochloride for previously treated metastatic colorectal cancer

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
Appropriateness	Servier Laboratories	*Would it be appropriate to refer this topic to NICE for appraisal?* Yes	Comment noted.
Wording	Servier Laboratories	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?* No. The wording of the remit does not reflect the anticipated indication for trifluridine in combination with tipiracil (Lonsurf), therefore the outcome of the appraisal may not appropriately reflect the marketing authorisation for the product. This is particularly relevant to the section of the remit which states "..after at least 2 prior chemotherapy regimens". The current anticipated wording of the licence is as follows: Lonsurf is indicated 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 including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy.	The remit has been updated to reflect the anticipated marketing authorisation.

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		Therefore it is proposed that the wording of the remit should be "To appraise the clinical and cost effectiveness of trifluridine in combination with tipiracil (Lonsurf) within its marketing authorisation for treating metastatic colorectal cancer."	
Timing Issues	Servier Laboratories	[redacted]	Comment noted.
Additional comments on the draft remit	Servier Laboratories	No	Noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Servier Laboratories	The background information should be amended to reflect the recent statement from the Cancer Drugs Fund that the following technologies are due to delisted from the approved list on 5th November 2015: 1. Bevacizumab in combination with oxaliplatin-based chemotherapy in the second and third line settings 2. Cetuximab monotherapy for third and fourth line settings 3. Panitumumab monotherapy for third and fourth line settings Regorafenib has recently been licensed for the treatment of patients of metastatic colorectal cancer (CRC) who have been previously treated with or are not considered candidates for available therapies. It is not recommended by NICE due to a terminated appraisal but is a recommended 3rd line or later option in the European Society for Medical Oncology Guidelines.[1]	The background section has been updated to reflect current clinical practice in England.

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		Reference 1. Van Cutsem et al. Metastatic colorectal cancer:ESMO Clinical Pratice Guidelines for diagnosis, treatment and follow up. Annals of Oncology 25 (supplement 3): iii1-iii9, 2014 doi:10.1093/annonc/mdu260	
The technology/ intervention	Servier Laboratories	*Is the description of the technology or technologies accurate?* Yes	Comment noted
Population	Servier Laboratories	As stated above in the comments on the remit the reference to "..after at least 2 prior chemotherapy regimens", is not reflective of the anticipated licensed indication and should therefore be removed or amended. Therefore it is proposed that the population is defined as follows: Adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy.	The population has been updated to reflect the anticipated marketing authorisation.
Comparators	Servier Laboratories	*Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared?* No. The anticipated licensed indication for trifluridine in combination with tipiracil (Lonsurf) states that patients (if appropriate) would have already received an anti-VEGF biological therapy, and an anti-EGFR therapy, prior to consideration for the product. Therefore, Bevacizumab, Cetuximab and Panitumumab (although not currently listed as a comparator) would not be appropriate comparators for this appraisal. Raltitrexed is not used in the line of therapy being considered in this appraisal. Raltitrexed is only used in patients intolerant of 5FU by virtue of chest pain or other cardiac complications. Therefore, it is not a relevant	Consistent with the updated remit and population, the comparators have been amended to specify 'best supportive care' as the only comparator.

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		comparator for this appraisal.[2] Regorafenib has recently been licensed for metastatic colorectal cancer and could be considered as a comparator in this appraisal, given that the licence is very similar to trifluridine in combination with tipiracil (Lonsurf). Regorafenib is indicated 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 fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy.3 It is noted that Regorafenib is not recommended by NICE due to a terminated appraisal, but is a recommended 3rd line or later option in the European Society for Medical Oncology Guidelines.[1] Best supportive care is an appropriate comparator References 1. Van Cutsem et al. Metastatic colorectal cancer:ESMO Clinical Pratice Guidelines for diagnosis, treatment and follow up. Annals of Oncology 25 (supplement 3): iii1-iii9, 2014 doi:10.1093/annonc/mdu260 2. Expert Opinion – Medical Oncologist 3. Summary of Product Characteristics; Stivarga. EMC+ available at www.medicines.org.uk last accessed September 2015	
Outcomes	Servier Laboratories	Response rates are usually less than 10% for second line therapies in patients with metastatic colorectal cancer, therefore are likely to be extremely low at 3rd line or beyond. Hence, inclusion of this endpoint is unlikely to be meaningful.[2]	Comment noted. 'Response rate' is a standard outcome measure for technology appraisals of cancer drugs. No changes to the scope have been

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		Reference 2. Expert Opinion - Medical Oncologist	made.
Economic analysis	Servier Laboratories	The time horizon should be lifetime	Comment noted.
Equality and Diversity	Servier Laboratories	No comments	Noted.
Innovation	Servier Laboratories	No comments	Noted.
Other considerations	Servier Laboratories	The appraisal remit etc. should be in line with and reflect the anticipated marketing authorisation	The remit and population have been updated to reflect the anticipated marketing authorisation.
Questions for consultation	Servier Laboratories	Question: How is trifluridine in combination with tipiracil hydrochloride expected to be used in clinical practice? Is it expected to be used after specific chemotherapy regimens or lines of treatment? In line with the anticipated licence indication i.e. in patients who previously been treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy Question: Which treatments are considered to be established clinical practice in the NHS for metastatic colorectal cancer in people after at least 2 prior chemotherapy regimens?	Comments noted. Consistent with the updated remit and population, the comparators have been amended to specify 'best supportive care' as the only comparator. No subgroups are specified in the scope.

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		Following the recent announcement from the CDF, there will be no recommended 3rd line treatment for metastatic colorectal cancer in the UK from 5th November 2015. Therefore patients would receive best supportive care. Question: Are there any subgroups of people in whom trifluridine in combination with tipiracil hydrochloride is expected to be more clinically effective and cost effective or other groups that should be examined separately? - Should consideration be given to RAS mutation status or any other biological markers? No. The RECOURSE study included patients with both wild-type (49%) and mutant (51%) tumours. 4 The efficacy of trifluridine in combination with tipiracil hydrochloride (Lonsurf) was demonstrated across both subgroups Question: Where do you consider trifluridine in combination with tipiracil hydrochloride will fit into the existing NICE pathway, Colorectal cancer? Trifluridine in combination with tipiracil hydrochloride (Lonsurf) is expected to be used following the first and second line options in the NICE pathway.5 References 4. Mayer RJ et al. Randomised Trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015;372:1909-19 5. Colorectal cancer pathway available at www.pathways.nice.org.uk last accessed September 2015	

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Additional comments on the draft scope	Royal College of Radiologists	Thank you for the opportunity for The Royal College of Radiologists (RCR) to comment on the draft scope for the Appraisal of Trifluridine for previously treated metastatic colorectal cancer. The RCR has the following comments for inclusion in the joint response to NICE: • The RCR notes that, to our knowledge, Trifluridine does not yet have a licence. Is that correct? • There are no established 3rd-line regimes. All of the below may be used. • The RCR feels that not all of the relevant comparators are listed. We suggest they should be: o FOLFIRI o FOLFOX o XELIRI o XELOX o Cetuximab alone o Cetuximab/irinotecan o Panitumumab o Regorefanib o Aflibercept o Mitomycin C/5fu infusion (COMBAT regime) o XELOX/bevacizumab o FOLFOX/bevacizumab o S1 • The RCR suggests that Raltitrexed should not be included as it is only	Comments noted. At the time of writing, trifluridine in combination with tipiracil does not have a marketing authorisation. Consistent with the updated remit and population (based on the anticipated marketing authorisation), the comparators have been amended to specify 'best supportive care' as the only comparator. Because of this, RAS status is unlikely to affect treatment options, so is not a relevant subgroup. No subgroups are specified in the scope.

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		used for patients who have cardiac complications with other drugs. • We suggest that RAS status should be considered as it limits other options. • The RCR feels that location of metastases is not relevant. • If approved, Lonsurf would fit in to the NICE pathway according to its licence.	
	Servier Laboratories	No	Noted.

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

Department of Health
Merck Serono
Pfizer
Roche Products
Royal College of Pathologists