National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Aflibercept in combination with irinotecan and fluorouracil-based therapy for the treatment of metastatic colorectal cancer which has progressed following prior oxaliplatin-based chemotherapy

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	Sanofi	Sanofi believe that an appraisal of aflibercept in this indication is appropriate	Comment noted, no action required
	Roche Products Limited	This topic is appropriate	Comment noted, no action required
	NCRI Colorectal CSG/RCP/RCR/ACP/JCCO	Data has been presented at ASCO meeting. However, this has not yet been published and it is therefore still early time point for this review	NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	CSAS	This is appropriate.	Comment noted, no action required
	Bowel Cancer UK	The remit seems appropriate for the appraisal. It would be interesting to know, however, why Aflibercept is not licensed/being appraised in combination with Oxaliplatin based chemotherapy regimens, e.g. FOLFOX.	NICE can only issue guidance within the licensed indications for a technology. The remit for the appraisal reflects the anticipated licence and the clinical trial data - in a phase III trial (NCT00561470) aflibercept in combination with

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			FOLFIRI is being compared with placebo plus FOLFIRI.
	NHS North Yorkshire & York	This is appropriate.	Comment noted, no action required
Wording	Sanofi	The remit is appropriate.	Comment noted, no action required
	Roche Products Limited	Yes	Comment noted, no action required
	CSAS	It is essential that aflibercept be compared with treatments currently recommended for use in the NHS. It must therefore be compared with irinotecan monotherapy as second-line therapy for patients with metastatic colorectal cancer, which has progressed after (or failed to respond to) oxaliplatin-based treatments as this has been recommended by NICE in TA93	It was agreed at the scoping workshop that irinotecan monotherapy is not used in clinical practice for the population defined in the scope as it is usually reserved for people not able to tolerate further fluorouracil based therapy, and should not therefore be a comparator.
	Bowel Cancer UK	The wording of the remit appears appropriate for the review, with the above caveat re the non-appraisal of the treatment with Oxaliplatin based chemotherapy regimens.	Comment noted no action required.
	NHS North Yorkshire & York	It is essential that aflibercept be compared with treatments currently recommended for use in the NHS. It must therefore be compared with irinotecan monotherapy as second-line therapy for patients with metastatic colorectal cancer, which has progressed after (or failed to respond to) oxaliplatin-based treatments as this has been recommended by NICE in TA93.	It was agreed at the scoping workshop that irinotecan monotherapy is not used in clinical practice for the population defined in the scope as it is usually reserved for people not able to tolerate further

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			fluorouracil based therapy, and should not therefore be a comparator.
Timing Issues	Sanofi	Sanofi believes that the timing of this appraisal is appropriate given that there are no agents with evidence of clinical benefit in the post-oxaliplatin treated patient population. [redacted]	Comment noted.
	Roche Products Limited	No comment	Noted, no action required
	NCRI Colorectal CSG/RCP/RCR/ACP/JCCO	Not urgent.	Comment noted, no action required
	CSAS	Further data could be available from the manufacturer when ongoing RCTs complete in Oct' 11.	Comment noted, no action required
	Bowel Cancer UK	Aflibercept is the first new, effective, CRC treatment to appear on the market for several years, and follows a period in which NICE has turned down many CRC treatments on cost grounds. It would be helpful, therefore, if the treatment is appraised urgently, to help future patients who might benefit from it.	Comment noted, no action required
	NHS North Yorkshire & York	Further data could be available from the manufacturer when ongoing RCTs complete in Oct' 11.	Comment noted, no action required
Additional comments on the draft remit		No response received	Response noted

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Sanofi	Sanofi believe the background information to be accurate.	Comment noted, no action required
	Roche Products Limited	No comment	Noted, no action required
	NCRI Colorectal CSG/RCP/RCR/ ACP/JCCO	Nil to add	Comment noted, no action required
	CSAS	This is complete.	Comment noted, no action required
	Bowel Cancer UK	I was wondering if it was possible to find out where this 12% had come from as I have been using CRUK's figure for 5-year survival of metastasized colorectal cancer of 6.6%. I want to make sure we haven't missed the publication of some new data.	Comment noted. The 12% five year survival rate was based on data from Wessex Colorectal Cancer Audit, 1999. We have updated the scope to reflect the recent information provided.
	NHS North Yorkshire & York	This is complete.	Comment noted, no action required
The technology/ intervention	Sanofi	Sanofi believe the description of the technology could be made more precise: Aflibercept (VEGF-Trap, Sanofi and Regeneron Pharmaceuticals) is a recombinant fusion protein that binds to vascular endothelial growth factor-A and B (VEGF-A, VEGF-B), and Placental Growth Factor isoforms (PLGF1, PLGF2), thereby preventing the growth of new capillary blood vessels. Rationally designed to block a network of angiogenesis pathways, aflibercept reduces vascularisation of tumours and inhibits tumour growth. It is administered by intravenous infusion.	The scope has been updated to reflect the comments.

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		The only change, is that we have removed the phrase 'fully human' from the technology description section. This phrase has been debated internally as to its additive descriptive value; we were unsure when we submitted the file last week what conclusion our colleagues had reached on this. As a consequence of their decision to exclude it from the proposed regulatory labels, we now consider it helpful to remove it from the draft scope.	
	Roche Products Limited	Yes	Comment noted, no action required
	NCRI Colorectal CSG/RCP/RCR/ ACP/JCCO	Nil to add	Comment noted, no action required
	CSAS	This is accurate.	Comment noted, no action required
	NHS North Yorkshire & York	This is accurate.	Comment noted, no action required
Population	Sanofi	[redacted]	Comment noted, thanks for providing the information
	Roche Products Limited	Yes	Comment noted, no action required
	NCRI Colorectal CSG/RCP/RCR/ ACP/JCCO	Given the additional toxicities then a cautious approach should be taken in stipulating who is fit to receive palliative chemotherapy with aflibercept	Scoping workshop attendees discussed whether there is any sub-population which would be more prone to the additional toxicities associated with aflibercept and which

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			needs to be excluded from the scope. It was agreed that it is not possible to define this with limited available data at this stage.
	CSAS	This must include patients who have received first-line therapies that are recommended for use in the NHS (e.g. in NICE TA 93 and TA 61).	In the phase III trial (NCT00561470) aflibercept plus FOLFIRI is being studied in people with metastatic colorectal cancer who have received only one prior line of treatment consisting of an oxaliplatin-based regimen and it is likely that the population in the marketing authorisation will reflect the population in the trial. NICE can only issue guidance within the licensed indications of a technology.
	NHS North Yorkshire & York	This must include patients who have received first-line therapies that are recommended for use in the NHS (e.g. in NICE TA 93 and TA 61).	In the phase III trial (NCT00561470) aflibercept plus FOLFIRI is being studied in people with metastatic colorectal cancer who have received only one prior line of treatment consisting of an oxaliplatin-based regimen and it is likely that the population in the marketing authorisation will reflect the population in the trial. NICE can only issue guidance within the licensed

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			indications of a technology.
Comparators	Sanofi	Sanofi believe irinotecan and fluorouracil-based therapy is the appropriate comparator and this is what has been investigated in the VELOUR clinical trial. Sanofi however, do not agree that irinotecan monotherapy is an appropriate comparator. Irinotecan monotherapy is not an appropriate comparator for the following reasons; i) irinotecan monotherapy is usually reserved for patients who are not fit enough to receive irinotecan in combination with fluorouracil-based therapy indeed the license for irinotecan monotherapy states it is for patients who have failed a 5-FU based regimen. Given that the patients included in the VELOUR trial had to be fit enough to receive FOLFIRI (the combination of 5FU/LV plus irinotecan), irinotecan as a single agent would not be considered an appropriate option for them. ii) whilst irinotecan monotherapy in 2nd line mCRC has received positive approval by NICE, it is not considered to be routine, having been superseded by FOLFIRI – IMS data suggests current usage is only 3% of all 2nd line mCRC chemotherapy.	It was agreed at the scoping workshop that irinotecan monotherapy should not be considered as a comparator for this appraisal and the scope has been amended to reflect that.
	Roche Products Limited	XELIRI (Xeloda + Irinotecan) is also a licensed indication for this population and should be considered a comparator.	The clinical specialist at the scoping workshop advised that XELIRI is not routinely used for the population defined in the scope and should not be included as a comparator.
	NCRI Colorectal CSG/RCP/RCR/ ACP/JCCO	Our experts consider it essential that second line use of bevacizumab is considered a comparator despite a lack of phase III evidence in combination with irinotecan in second line where there are large sets of case series data. It	NICE Technology Appraisal Guidance 212 does not recommend bevacizumab in

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		is within the license of use of bevacizumab and is being funded in this situation broadly throughout England as part of the CDF	combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for metastatic colorectal cancer. Further, NICE can not specify the use of a technology not recommended in NICE guidance as a prior treatment.
	CSAS	FOLFIRI is not currently recommended as second-line chemotherapy. It is uncertain if other fluorouracil-based therapies in combination with irinotecan are in clinical use. It is therefore essential that aflibercept be assessed in comparison to irinotecan monotherapy or other second-line therapies in use in the NHS.	It was agreed at the scoping workshop that FOLFIRI is the standard treatment for the population defined in the scope. It was also agreed at the scoping workshop that irinotecan monotherapy should not be considered as a comparator for this appraisal as it is usually reserved for people not able to tolerate further fluorouracil based therapy.
	NHS North Yorkshire & York	FOLFIRI is not currently recommended as second-line chemotherapy. It is uncertain if other fluorouracil-based therapies in combination with irinotecan are in clinical use. It is therefore essential that aflibercept be assessed in comparison to irinotecan monotherapy or other second-line therapies in use in the NHS.	It was agreed at the scoping workshop that FOLFIRI is the standard treatment for the population defined in the scope. It was also agreed at the scoping workshop that

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			irinotecan monotherapy should not be considered as a comparator for this appraisal as it is usually reserved for people not able to tolerate further fluorouracil based therapy.
Outcomes	Sanofi	Sanofi agree that the outcome measures listed in the draft scope will capture the most important health related benefits associated with aflibercept.	Comment noted, no action required
	Roche Products Limited	Yes	Comment noted, no action required
	NCRI Colorectal CSG/RCP/RCR/ ACP/JCCO	Yes	Comment noted, no action required
	CSAS	Overall survival is the most important outcome, particularly as currently 5-year survival is very low at 12%. The formal assessment of quality of life is also essential, particularly if consideration will be given to progression-free survival or time to progression.	Comment noted, no action required
	NHS North Yorkshire & York	Overall survival is the most important outcome, particularly as currently 5-year survival is very low at 12%. The formal assessment of quality of life is also essential, particularly if consideration will be given to progression-free survival or time to progression.	Comment noted, no action required
Economic analysis	Sanofi	Sanofi agree that this is appropriate.	Comment noted, no action required
	Roche Products Limited	No Comment	Noted, no action required
	NCRI Colorectal CSG/RCP/RCR/	The main issue here is that one might sum up the outcome of the appraisal. We have only one phase III trial for aflibercept and confusing data. In terms of cost analysis compared to irinotecan based therapy without bevacizumab then	NICE recommendations are based on clinical and cost-effectiveness of new health

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	ACP/JCCO	there is only one answer possible from NICE unless the cost of the drug is to be highly competitive. There is significant risk of the bizarre situation reoccuring where a negative NICE appraisal takes place but then funding is possible on the CDF in a highly heterogenous manner within in England. This must be avoided.	technologies and not on cost analysis as suggested. Issue of non uniform funding by Cancer Drug Fund is outside the remit of a technology appraisal.
	CSAS	With current 5-year survival at 12%, it would not be reasonable to consider a time horizon beyond 5 years, as too little empirical data would be available for robust modelling.	NICE recommends use of a life time horizon if the technology affects survival at differential rate when compared with the relevant comparator. A time horizon shorter than lifetime could only be justified if there is no differential mortality effect between options, and the differences in costs and HRQL relate to a relatively short period (for example, in the case of an acute infection). For details see Guide to the methods of technology appraisal page 33. For a lifetime horizon extrapolation modelling with scenario analyses reflecting different assumptions is often necessary and acceptable for Committee deliberations.
	NHS North Yorkshire &	With current 5-year survival at 12%, it would not be reasonable to consider a time horizon beyond 5 years, as too little empirical data	NICE recommends use of a life time horizon if the technology affects survival at

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	York	would be available for robust modelling.	differential rate when compared with the relevant comparator. A time horizon shorter than lifetime could only be justified if there is no differential mortality effect between options, and the differences in costs and HRQL relate to a relatively short period (for example, in the case of an acute infection). For details see Guide to the methods of technology appraisal page 33. For a lifetime horizon extrapolation modelling with scenario analyses reflecting different assumptions is often necessary and acceptable for Committee deliberations.
Equality	Sanofi	Sanofi is not aware of any factors relating to the use of aflibercept that might lead to discrimination.	Comment noted, no action required
	Roche Products Limited	No Comment	Comment noted, no action required
	NCRI Colorectal CSG/RCP/RCR/ ACP/JCCO	This should actually relate to where they live as a more specific issue	Issue of non uniform availability of cancer drugs funded by other organizations is outside the remit of a technology appraisal.
	CSAS	No issues.	Comment noted, no action

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			required
	NHS North Yorkshire & York	No issues.	Comment noted, no action required
Other considerations	Sanofi	No response received	Noted
	Roche Products Limited	No Comment	Noted, no action required
	NCRI Colorectal CSG/RCP/RCR/ ACP/JCCO	No license yet exists - application will be forthcoming	Comment noted, no action required
	CSAS	As this is another anti-VEGF drug, it might be appropriate to find out whether other anti-VEGF drugs will be marketed for metastatic colorectal cancer (particularly second-line) in the near future and undertake a multiple technology appraisal when sufficient evidence is available.	It was agreed at the scoping workshop that a single technology appraisal (STA) is appropriate for this appraisal.
	NHS North Yorkshire & York	As this is another anti-VEGF drug, it might be appropriate to find out whether other anti-VEGF drugs will be marketed for metastatic colorectal cancer (particularly second-line) in the near future and undertake a multiple technology appraisal when sufficient evidence is available.	It was agreed at the scoping workshop that STA is appropriate for this appraisal
Innovation	Sanofi	**Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** However captured, it is likely that the QALY would fail to capture significant patient benefits. The positive experience for patients and their relatives of being able to continue to fight their disease, rather than palliate their condition in its final stages, is a significant and important psychological benefit of aflibercept that would not be captured directly by the EQ-5D tool, and consequently is not fully	The appraisal will be completed in accordance with NICE's published methods guide. The EQ-5D tool includes anxiety and depression as one of its dimensions. However if the EQ-5D tool is considered to be inappropriate, empirical evidence should be provided

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		incorporated in the QALY measure. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits** To understand the importance to patients and their families of actively challenging mCRC in the second-line setting, and the psychological impact that the treatment with aflibercept can deliver, we consider the testimony of patients, family members and clinicians should be sought by the committee. **Do you consider the technology 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)?** Aflibercept can be considered an innovation for the following reasons: i) Aflibercept is the first drug with a mechanism of action that targets the three angiogenic factors (VEGF-A, VEGF-B and PLGF), all of which are believed to play important roles in the angiogenesis pathway ii) Aflibercept is the first anti-angiogenic therapy to show an overall survival benefit in mCRC patients who have been treated with an oxaliplatin-based therapy. iii) Aflibercept is the first anti-angiogenic therapy to show benefit in mCRC patients previously treated with another anti-angiogenic therapy.	on why the properties of the EQ-5D are not suitable for the particular patient population. Further, the Institute is interested in capturing a range of patient and carer views on, and experiences of, living with the condition, and the impact of a technology on a patient's symptoms and physical, social, psychological and emotional state. Comments noted.
	Roche Products	No Comment	Noted, no action required

Section	Consultees	Comments	Action
	Limited		
	NCRI Colorectal CSG/RCP/RCR/ ACP/JCCO	Seems to be a fairly similar drug in terms of benefits to bevacizumab, with subtly differing mode of action. Cost will remain the main issue especially as there appear to be greater toxicity issues with this drug compared to bevacizumab	Comment noted, no action required
	CSAS	No, this is another example of an anti-VEGF drug. These are already in use in a number of other clinical situations.	Comment noted, no action required
	NHS North Yorkshire & York	No, this is another example of an anti-VEGF drug. These are already in use in a number of other clinical situations.	Comment noted, no action required
Questions for consultation	Sanofi	**Have the most appropriate comparators for aflibercept been included in the scope? Are there any other comparators routinely used in clinical practice?** Yes, irinotecan and fluorouracil-based therapy are the appropriate comparators. **Will the intervention be given only in combination with irinotecan?** [redacted] **Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality?** Not known	Comment noted, no action required
	Roche Products Limited	No Comment	Noted no action required
	NHS North	No, this is another example of an anti-VEGF drug. These are already in use in	Comment noted, no action

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	Yorkshire & York	a number of other clinical situations.	required
Additional comments on the draft scope		No response received	Noted, no action required

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

Royal College of Nursing
Royal College of Pathologists
Welsh Government
BASO ~ The Association for Cancer Surgery
Department of Health
Medicines and Healthcare products Regulatory Agency