National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Aflibercept for treating myopic choroidal neovascularisation

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	Bayer	Bayer believes that it is appropriate to refer this topic to NICE for appraisal. Typically, mCNV affects adults aged 40-50 years and has a poor prognosis, especially if left untreated, resulting in progressive and irreversible loss of visual acuity, particularly central vision, and leading to blindness. There is currently no cure for mCNV, and the key management strategy is to maintain visual capability for the daily activities such as driving, working, reading and writing. Prompt diagnosis and treatment is particularly important due to pathological myopia affecting younger patients of working age. Ranibizumab (an alternative anti-vascular endothelial growth factor (VEGF) therapy) has been appraised by NICE in this indication (Technology Appraisal 298, published November 2013). Bayer plan to market aflibercept in mCNV from early 2017.	Comments noted. No action required.
	Novartis Pharmaceuticals	Yes, it is appropriate for this topic to be referred.	Comments noted. No action required.

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	Royal College of Ophthalmologists	Loss of vision due to myopia is of significant concern as it can occur at a relatively young age and the incidence of myopia is increasing, especially in some ethnic groups such as Chinese. The development of choroidal neovascular membranes associated with myopia can course a rapid loss of vision so the availability of treatment is important and so this is appropriate for NICE appraisal.	Comments noted. No action required.
Wording	Bayer	Yes, the wording of the remit reflects the issue of clinical and cost effectiveness about this technology that NICE should consider.	Comments noted. No action required.
	Novartis Pharmaceuticals	Yes	Comments noted. No action required.
	Royal College of Ophthalmologists	Yes	Comments noted. No action required.
Timing Issues	Bayer	Bayer plans to market aflibercept in mCNV in England and Wales from early 2017, although the UK marketing authorisation was issued for this indication in October 2015.	Comments noted. No action required.
	Novartis Pharmaceuticals	No comment	Comments noted. No action required.
	Royal College of Ophthalmologists	Ranibizumab is approved so this would be an alternative treatment. Biologically aflibercept is a more potent anti VEGF so it may have advantages although it hasn't been directly compared. In diabetic macular oedema (Protocol T, DRCR.net; aflibercept has been shown to be more effective than	Comments noted. NICE can only begin to appraise a technology when it has been

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		ranibizumab so there is clinical evidence of it being more effective, as myopia especially can be a problem at a younger age access to the best treatments would be advisable so it should be given some priority.	formally referred by the Secretary of State for Health.
Additional comments on the draft remit	Bayer	None.	Comments noted. No action required.

Comment 2: the draft scope

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Background information	Bayer	Regarding the prevalence - a recent systematic review suggests the prevalence of pathological myopia (PM) is 1–3% in adults (1). Myopic CNV occurs in 5-11% of patients with PM (2). In addition, the numbers quoted for patients in England with myopia (>300,000) should refer to patients with pathological myopia (see Table 1 of referenced costing statement). Bayer questions the validity of the following statement: 'Verteporfin photodynamic therapy is also used in clinical practice for treating subfoveal CNV associated with pathological myopia.' Market research of 52 UK ophthalmologists who treat mCNV conducted by Bayer in January 2016 shows that in current clinical practice, only [redacted] of patients are treated with vPDT.	Comments noted. The background section in the scope has been updated.

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		Regarding the following statement: 'Bevacizumab does not have a marketing authorisation in the UK for treating eye conditions but it is used off-label in clinical practice.' Bevacizumab is reformulated for use in the eye and is therefore not licensed in this indication. There is a difference between being used off-label and being unlicensed so the wording should be amended. (1) Wong TY, Ferreira A, Hughes R. Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: an evidence-based systematic review. Am J Ophthalmol 2014;157:9-25 (2) Wong TY, Ohno-Matsui K, Leveziel N, Holz FG, Lai TY, Yu HG, et al. Myopic choroidal neovascularisation: current concepts and update on clinical management. Br J Ophthalmol 2015;99(3):289-96.	
	Novartis Pharmaceuticals	The information is appropriate.	Comments noted. No action required.
	Royal College of Ophthalmologists	Incidence figures will vary depending on the ethnic mix as this is more common in Asians so some information on this could be considered.	Comments noted. The background section in the scope has been updated.
The technology/ intervention	Bayer	Yes – the description of the technology is accurate.	Comments noted. No action required.
	Novartis Pharmaceuticals	No comment.	Comments noted. No action required.

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	Royal College of Ophthalmologists	Yes	Comments noted. No action required.
Population	Bayer	The population is defined appropriately. There are no groups within this population that should be considered separately.	Comments noted. No action required.
	Novartis Pharmaceuticals	The population is appropriate.	Comments noted. No action required.
	Royal College of Ophthalmologists	Incidence of myopia is higher in some ethnic groups such as Asians and is increasing in all groups. Choridal neovascular membranes associated with myopia should be considered not just whether the myopia is higher than -6 (pathological) as this group is just the group that this is more likely to happen in but this does not occur exclusively in this group.	Comments noted. Aflibercept will be appraised within its marketing authorisation for treating myopic choroidal neovascularisation.
Comparators	Bayer	Bayer considers that the most appropriate comparator is ranibizumab (Lucentis) as it is used in the majority of patients. Ranibizumab (an alternative anti-VEGF therapy) has been appraised by NICE in this indication (Technology Appraisal 298). vPDT is not an appropriate comparator as it is not standard treatment within the NHS for mCNV. In addition, bevacizumab is not an appropriate comparator for aflibercept in mCNV - it cannot be considered routine practice as its usage is low and it is unlicensed for use in the eye.	Comments noted. When selecting the most appropriate comparator(s), the committee will consider: • established NHS practice in England

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			• the natural history of the condition without suitable treatment • existing NICE guidance • cost effectiveness • the licensing status of the comparator. The appraisal committee can consider as comparators technologies that do not have a marketing authorisation (or CE mark for medical devices) for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS. For more details, please see sections 6.2.1–6.2.4 of NICE's guide to

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			the methods of technology appraisal (2013).
	Novartis Pharmaceuticals	Ranibizumab and verteporfin photodynamic therapy are appropriate licensed comparators. Bevacizumab has not been formally assessed by regulators for ophthalmic use. Therefore, it is an unlicensed and unregulated treatment for this indication and is not an appropriate comparator in this appraisal.	Comments noted. When selecting the most appropriate comparator(s), the committee will consider: • established NHS practice in England • the natural history of the condition without suitable treatment • existing NICE guidance • cost effectiveness • the licensing status of the comparator. The appraisal committee can consider as comparators technologies that do not have a marketing authorisation (or CE

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			mark for medical devices) for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS. For more details, please see sections 6.2.1–6.2.4 of NICE's guide to the methods of technology appraisal (2013).
	Royal College of Ophthalmologists	Ranibizumab is now the standard of care as it is a licensed drug that is NICE approved for this indication. Photodynamic therapy is now rarely used of this indication and would only be a second line use or if injections were not possible or deemed unsafe. Bevacizumab is not licensed and should not be used where this is a licensed alternative by the NHS, so whilst it is used on occasion, not usually where NHS funding is in place for ranibizumab and so I don't think it should be used as a comparator as the NHS is not in a position to use avastin, as is the case with macular degeneration.	Comments noted. When selecting the most appropriate comparator(s), the committee will consider: • established NHS practice in England • the natural history of the condition without suitable treatment

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			• existing NICE guidance • cost effectiveness • the licensing status of the comparator. The appraisal committee can consider as comparators technologies that do not have a marketing authorisation (or CE mark for medical devices) for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS. For more details, please see sections 6.2.1–6.2.4 of NICE's guide to the methods of technology appraisal (2013).

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Outcomes	Bayer	In addition to the outcomes proposed, Bayer will, subject to the availability of suitable data, present on: • Change in central retinal thickness (CRT) • Proportion of patients gaining or losing ≥ 15, ≥ 10, or ≥ 5 ETDRS letters • Absolute change in CNV lesion size • Change in Leakage from CNV Bayer will not be presenting data on contrast sensitivity as this was not collected in the pivotal study.	Comments noted. The outcomes specified in the scope are consistent with the outcomes specified across all NICE technology appraisals of technologies for treating eye conditions. Other clinically relevant outcomes may be included in the company's submission provided sufficient rationale is given to support direct health effects for patients. Also, any deviation from the scope will need to be clearly explained in the company's submission. No changes to the scope.
	Novartis Pharmaceuticals	The outcomes are adequate.	Comments noted. No action required.

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	Royal College of Ophthalmologists	Yes but it needs to be borne in mind when considering first and second affected eyes that at the time of treating a first eye the benefit is hard to demonstrate as the unaffected eye will have good vision but this eye may get affected at a later date and both eyes may not respond so well to treatment. It is important to maximise the benefit for the patient especially as this condition often occurs at a younger age. Incidence of visual loss in both eyes and risk of second eye visual loss need to be considered as part of this analysis.	Comments noted. The analysis of clinical effectiveness must be based on data from all relevant studies of the best available quality and should consider the range of typical patients, normal clinical circumstances, clinically relevant outcomes, comparison with relevant comparators, and measures of both relative and absolute effectiveness with appropriate measures of uncertainty. All parameters used to estimate clinical and cost effectiveness should be presented clearly in tabular form and include details of data sources. For all parameters (including effectiveness, valuation

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			of health-related quality of life and costs) economic evaluation should systematically consider possible data sources, and avoid selection bias in the choice of sources.
Economic analysis	Bayer	Bayer proposes that the economic evaluation will take the form of a cost utility analysis with results expressed in terms of incremental cost per quality-adjusted life year. The time horizon will be lifetime and costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account, although Bayer does not know and does not want to know the PAS price of ranibizumab. The model considers both eyes although it should be noted that in the pivotal study, only one eye was designated as the study eye. For subjects who met eligibility criteria in both eyes, the eye with the worst VA was selected as the study eye.	Comments noted. When a reduced price is available through a patient access scheme that has been agreed with the Department of Health, the base-case analysis should include the costs associated with the scheme.
	Novartis Pharmaceuticals	No comment	Comments noted. No action required.
	Royal College of Ophthalmologists	Chroroidal neovascular membranes due to myopia tend to respond well with few injections. Atrophy also develops as part of myopic macular degeneration	Comments noted. Many technologies have

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		that can affect benefit in the longer term and maybe asymmetric between eyes so is part of the argument about why each eye should be treated on its merits and not given less value if the other eye is ok. Longer term modelling therefore needs to be considered although longer term evidence of benefit may not be available.	impacts on costs and outcomes over a patient's lifetime. For a lifetime time horizon, it is often necessary to extrapolate data beyond the duration of the clinical trials and to consider the associated uncertainty. When the impact of treatment beyond the results of the clinical trials is estimated, analyses that compare several alternative scenarios reflecting different assumptions about future treatment effects using different statistical models are desirable. For more details, please see sections 5.1.16 and 5.7.7 of NICE's guide to the methods of technology appraisal (2013).

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Equality and Diversity	Bayer	We are not aware of any potential equality issues related to the appraisal.	Comments noted. No action required.
	Novartis Pharmaceuticals	No comment	Comments noted. No action required.
	Royal College of Ophthalmologists	As said earlier myopia is more common in some ethnic groups, particularly Asians. Myopia can be associated with deafness in some rarer genetic variants.	Comments noted. NICE is committed to advancing equality of opportunity, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and society as a whole, and to complying fully with its legal obligations on equality and human rights. When formulating its recommendations to the Institute, the appraisal committee has discretion to consider those factors it believes are most appropriate to

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			each appraisal. In doing so, the appraisal committee has regard to NICE's legal obligations on equality and human rights.
Other considerations	Bayer	None.	Comments noted. No action required.
	Novartis Pharmaceuticals	No comment	Comments noted. No action required.
Innovation	Bayer	Aflibercept tightly binds to all forms of VEGF and PlGF known to contribute to angiogenesis in the eye. In comparison ranibizumab is a recombinant, humanized, monoclonal antibody Fab fragment against VEGF-A. Thus, aflibercept binds tighter to VEGF than the natural receptors and currently available treatments: Stewart et al.(1) demonstrated that 79 days after a single Eylea (1.15 mg) injection, the intravitreal VEGF-binding activity would be comparable to ranibizumab at 30 days. This finding may be a potential advantage in terms of reducing the number of injections required. Suppression of anterior chamber VEGF has been reported for patients with neovascular age-related macular degeneration (AMD) and with visual impairment due to diabetic macular oedema (DMO):	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.

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		• A mean of 34–37 days (5–6 weeks) and less than 2 months in most patients with ranibizumab (2,3) • A mean of >69 days (10 weeks) with aflibercept in most patients (4,5) (1) Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol 2008 May;92(5):667-8. (2) Muether PS et al. Am J Ophthalmol 2013; 156 (5): 989–993; (3) Muether PS et al. Br J Ophthalmol 2014; 98 (2): 179–181; (4) Fauser S et al. Am J Ophthalmol 2014; 158 (3): 532–536; (5) Chan et al. Abstract presented at the 37th Annual Macula Society Meeting; Key Largo, FL, 19–22 February 2014.	
	Novartis Pharmaceuticals	No comment	Comments noted. No action required.
	Royal College of Ophthalmologists	Afibercept is different anti-VEGF to ranibizumab that has shown a clinically significant benefit for treating diabetic macular oedema so may also be moer beneficial than ranibizumab but I don't think that is proven. A choice of treatment in this potentially blinding condition that can affect people of working age would seem a good thing.	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.
NICE Pathways	Bayer	Bayer consider that aflibercept will be offered as an alternative to ranibizumab as an option for treating visual impairment due to choroidal neovascularisation secondary to pathological myopia.	Comments noted. No action required.

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Questions for consultation	Bayer	*Is afilbercept likely to be used in clinical practice for treating all adults with myopic choroidal neovascularisation, or only for adults with choroidal neovascularisation secondary to pathological myopia?* Aflibercept is licensed for the use in adults for the treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV). *Have all relevant comparators for aflibercept been included in the scope? Which treatments are considered to be established clinical practice in the NHS for myopic choroidal neovascularisation?* See Bayer's comments above regarding appropriate comparator. *Are the outcomes listed appropriate?* See Bayer's comments above regarding appropriate outcomes. *Are there any subgroups of people in whom aflibercept is expected to be more clinically effective and cost effective or other groups that should be examined separately?* None. *Do you consider aflibercept to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might*	Comments noted. No action required.

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		improve the way that current need is met (is this a 'step-change' in the management of the condition)? See Bayer's comments above regarding innovation. *Do you consider that the use of aflibercept can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* No comment. *NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process.* Bayer agrees that an STA is appropriate.	
	Novartis Pharmaceuticals	No comment	Comments noted. No action required.
Additional comments on the draft scope	Bayer	None.	Comments noted. No action required.
	Novartis Pharmaceuticals	None	Comments noted. No action required.

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	Royal College of Ophthalmologists	*Is afilbercept likely to be used in clinical practice for treating all adults with myopic choroidal neovascularisation, or only for adults with choroidal neovascularisation secondary to pathological myopia?* All patients as essentially if a choroidal neovascular membrane has developed then the eye would be defined as having pathological myopia from a clinical point of view even though they may not be >-6, which is often used as a cut of for epidemiological studies. *Have all relevant comparators for aflibercept been included in the scope? Which treatments are considered to be established clinical practice in the NHS for myopic choroidal neovascularisation?* Yes, Ranibizumab is established practice. *Are the outcomes listed appropriate?* Yes *Are there any subgroups of people in whom aflibercept is expected to be more clinically effective and cost effective or other groups that should be examined separately?* I don't think we have evidence to say it is more effective in one group to another but the condition is more common in some groups. So for incidence and long term outcomes without treatment then ethnic group is important.	Comments noted. Aflibercept will be appraised within its marketing authorisation for treating myopic choroidal neovascularisation.

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		Where do you consider aflibercept will fit into the existing NICE pathway, 'Eye conditions'? Retinal and macular conditions – choroidal neovascularisation (pathological myopia)	

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

- Department of Health