National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ranibizumab for the treatment of choroidal neovascularisation associated with pathological myopia

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

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Commissioning Support Appraisals Service	The topic is appropriate for consideration	Comment noted. Following discussion at the scoping workshop it was agreed that it was appropriate to seek a formal referral to appraise ranibizumab.
	Royal National Institute for the Blind	It is appropriate to refer this topic to NICE for appraisal. Currently patients with choroidal neovascularisation associated with pathological myopia (mCNV) have no treatment options and as a result lose their sight.	Comment noted. Following discussion at the scoping workshop it was agreed that it was appropriate to seek a formal referral to appraise ranibizumab.

Section	Consultees	Comments	Action
	Royal College of Nursing	It is not currently licensed for this indication as stated in the scope, but as it has been used 'off label'for a number of years clinicians have a good working knowledge of its efficacy. In addition research evidence demonstrates that it is more effective than the current licensed treatment for Photodynamic Therapy (PDT) therefore, it is appropriate and timely that NICE appraises its use for treatment of CNV in pathological myopia. Further, whilst the population affected is small in number it is viewed as an appropriate topic and treatment for consideration to maintain the health status of this population. Finally, reference to continuous employment status could also be considered.	Comment noted. Following discussion at the scoping workshop it was agreed that it was appropriate to seek a formal referral to appraise ranibizumab.
	Royal College of Pathologists	This referral is timely, relevant and should be considered a priority	Comment noted. Following discussion at the scoping workshop it was agreed that it was appropriate to seek a formal referral to appraise ranibizumab.
	Macular Disease Society	The referral is appropriate in our view	Comment noted. Following discussion at the scoping workshop it was agreed that it was appropriate to seek a formal referral to appraise ranibizumab.

Section	Consultees	Comments	Action
	Commissioning Support Appraisals Service	The wording of the draft scope is appropriate.	Comment noted.
Wording	Novartis	The licensed indication is expected to be [redacted]	Comment noted.
	Royal National Institute for the Blind	We are aware that the license for Lucentis for the treatment of mCNV is still pending. Perhaps the remit needs to reflect this.	Comment noted. The technology section of the scope states that ranibizumab does not currently have a UK marketing authorisation for the treatment of CNV associated with pathological myopia, however it has been studied in people with the condition.

Section	Consultees	Comments	Action
	Royal College of Nursing	Particular emphasis on the younger age group of this cohort of patients has been omitted. The fact that a high majority of them are employed and have dependants will have an impact on cost effectiveness calculations	Comment noted. The scope states that the time horizon for estimating the clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
	The Royal College of Ophthalmologists	The current remit states -To appraise the clinical and cost effectiveness of ranibizumab within its licensed indication for the treatment of choroidal neovascularisation associated with pathological myopia. Ranibizumab is not currently licensed for this indication. This point is stated correctly under the 'Technology' section	Comment noted.
	Royal College of Pathologists	Yes	Response noted.
	Macular Disease Society	Yes the wording is correct	Comment noted.

Section	Consultees	Comments	Action
	Commissioning Support Appraisals Service	Only one small RCT has published relevant results. Three additional relevant but unpublished RCTs were identified. The largest and most relevant RCT reported data collection was to be completed in April 2012. The results of this RCT will need to be available for consideration by NICE as additional evidence is limited. Ranibizumab does not currently have a European Marketing license for the indication under consideration.	Comment noted. The background section is only intended to provide a brief description of the disease and current management options. More complete information will be provided by the manufacturer in their submission once the appraisal begins.
Timing Issues	Royal National Institute for the Blind	It is very urgent that this proposed appraisal takes place. As mentioned above, patients currently have no treatment options and this topic could not be more timely. As with many sight conditions, the quicker a patient receives treatment for this eye condition the better the outcome will be. Many patients contact our helpline and tell us about the impact of this eye condition on their quality of life. Vision loss can prevent them from working, driving, reading and getting out and about. The current lack of treatment also causes a huge amount of anxiety for both the patient and their family.	Comment noted. If this topic is formally referred to NICE as a technology appraisal, innovation will be considered by the Committee when formulating its recommendations.
	Royal College of Nursing	Visual loss is rapid and permanent if not treated rapidly. As anecdotal and early research evidence shows a level of visual recovery when treated with Ranibizumab, it is essential that this proposed appraisal is addressed with some urgency to ensure no further loss of vision for those patients suffering with the disease.	Comment noted.

Section	Consultees	Comments	Action
	The Royal College of Ophthalmologists	Untreated CNV associated with myopia leads to progressive vision loss. This often occurs in the working age group (usually<50 years). Vision loss associated with CNV secondary to myopia is only reversible if promptly treated soon after onset. As such it is important that NHS treatment is promptly available to forstall permanernt visual loss.	Comment noted. Following discussion at the scoping workshop it was agreed that it was appropriate to seek a formal referral to appraise ranibizumab.
	Royal College of Pathologists	This is a little difficult to calibrate out of context but this is best regarded medium to high priority	Comment noted. Following discussion at the scoping workshop it was agreed that it was appropriate to seek a formal referral to appraise ranibizumab.
	Macular Disease Society	It is urgent in that the outcome of a NICE appraisal should be available as soon as possible after the granting of marketing authorisation so that patients can access treatment immediately. The NHS should be aware of this appraisal so that preparations can be made to ensure that eye clinics have capacity to treat the new patients.	Comment noted. Following discussion at the scoping workshop it was agreed that it was appropriate to seek a formal referral to appraise ranibizumab.
	Commissioning Support Appraisals Service	There is currently very limited published evidence from RCTs on which to assess the effectiveness of ranibizumab for this indication. The anticipated publication of a key phase III RCT (NCT01217944) will be important to the timing of this STA.	Comment noted.

Section	Consultees	Comments	Action
Additional comments on the draft remit			

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Commissioning Support Appraisals Service	Could not confirm figure of 200,000 people with pathological myopia in the UK. National Horizon Scanning Centre report states that CNV secondary to pathological myopia occurs in approximately 5-10% of such patients, and that prevalence rates for pathological myopia vary between 2 and 9% in different populations. In England (2009/10) pathological myopia resulted in 34 hospital admissions.	Comment noted. The incidence and prevalence of the condition was discussed at the scoping workshop. Attendees agreed that it is currently unknown what the exact prevalence and/or incidence of the condition is in the UK due to the limited published data.
	Novartis	The prevalence and incidence of pathological myopia (PM) in the UK population are not known. The basis of the estimate of 200,000 people with PM is not clear, and given the limited published epidemiological estimates, may not be accurate. Published data suggest a prevalence of CNV in patients with pathological myopia of 5-11%.	Comment noted. The incidence and prevalence of the condition was discussed at the scoping workshop. Attendees agreed that it is currently unknown what the exact prevalence and/or incidence of the condition is in the UK due to the limited published data.
	Royal National Institute for the Blind	It seems fine	Comment noted.
	Royal College of Nursing	Information regarding the clinical and cost effectiveness of Verteporfin photodynamic therapy should be referenced.	Comment noted. If the topic is referred to NICE for an appraisal, the Committee will consider evidence on the clinical and cost effectiveness of comparators.

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	The Royal College of Ophthalmologists	OK. However, it neeeds to be clarified that the 10% of pathologic myopes develop CNv over their lifetime (ie prevalence, NOT incidence). However, 30% of patients who develop CNV in one eye may develop a similar pathology in the other eye within 8 years	The incidence and prevalence of the condition was discussed at the scoping workshop. The prevalence of CNV in people with pathological myopia in the UK is likely to be less than 10%, because the estimate of 10% referred to in the draft scope came from a study of people from Southeast Asian origin, who have a higher prevalence of the condition compared with caucasian people. Attendees agreed that it is currently unknown what the exact prevalence and incidence of the condition is in the UK due to the limited published data
	Royal College of Pathologists	The background information is accurate and reasonably complete. I think it would be helpful, however, to reference the use of Lucentis for age-related macular degeneration and to mention the different age range affected by myopia	Comment noted. The background section is only intended to be a very brief overview. A more detailed description of the disease and treatment options will be submitted by the manufacturer and made available to the Committee.
	Macular Disease Society	We believe it to be accurate	Comment noted. No action required.
The technology/	CSAS	The description of the technology is accurate.	Comment noted. No action required.

Section	Consultees	Comments	Action
intervention	Royal National Institute for the Blind	It seems fine	Comment noted. No action required.
	Royal College of Nursing	Ranibizumab not only inhibits vascular growth but also permeability of those vessels which is relevant to control leakage from an already developed CNV.	Comment noted. The technology section of the scope briefly describes the mechanism of action of ranibizumab.
	The Royal College of Ophthalmologists	Yes	Comment noted.
	Royal College of Pathologists	Yes	Comment noted.
	Macular Disease Society	Yes	Comment noted.
Population	CSAS	Relevant RCTs have taken place in adult populations only (18 years and over).	Comment noted.
	Novartis	[redacted]	Comment noted.
	Royal National Institute for the Blind	The population seems fine. We are aware that choroidal neovascularisation associated with pathological myopia affects the working age population (people aged 40-60) and those of an Asian (Far East) decent. Perhaps these groups could be considered separately due to their risk.	Comment noted.
	The Royal College of Ophthalmologists	Yes, although NICE may consider extending the indication to all non-AMD CNV and not just myopia related CNV	Comment noted. The technology will be appraised within its licensed indication.
	Royal College of Pathologists	No	Response noted.

Section	Consultees	Comments	Action
	Macular Disease Society	Yes	Response noted.
Comparators	Commissioning Support Appraisals Service	RCTs have compared ranibizumab against verteporfin photodynamic therapy (VPT) and bevacizumab. The draft scope indicates some clinics use bevacizumab outside of its licensed indication, the extent to which this occurs, and represents standard treatment, is a consideration for each PCT.	Comment noted. The scoping workshop attendees stated that bevacizumab is routinely used in some centres in England and Wales, and is therefore an appropriate comparator.
	Novartis	vPDT is the current standard treatment and the appropriate comparator in this appraisal. Whilst unlicensed bevacizumab may be used in some centres, it is not routinely available and therefore not in routine or standard use. Given the lack of marketing authorisation, high quality randomised controlled trials and the variation in product quality due to local compounding, intravitreal bevacizumab cannot be described as best alternative care. Although a prospective, randomised case series comparing ranibizumab and bevacizumab has reported, this small pilot study included only 16 bevacizumab-treated eyes. In the absence of large, high quality trials of bevacizumab in myopic CNV, it is unlikely that the safety and efficacy profile will be sufficiently described to enable adequate comparisons of clinical or cost effectiveness.	Comment noted. The scoping workshop attendees stated that bevacizumab and verteporfin are routinely used in some centres in England and Wales, and they are therefore appropriate comparators.

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	Royal National Institute for the Blind	Patients and clinicians tell us that Verteporfin Photodynamic Therapy is not in routine use. The patients we speak to are not offered this treatment or told by their clinician that it will not work. Bevacizumab should not be used as a comparator as it is not licensed for use in the eye.	Comment noted. Section 2.24 of the Methods Guide states that comparator technologies may include those that do not have a marketing authorisation for the indication defined in the scope but that are used routinely for the indication in the NHS. The scoping workshop attendees stated that verteporfin and bevacizumab are routinely used in some centres in England and Wales, and are therefore appropriate comparators.
	Royal College of Nursing	PDT is highly effective in controlling CNV but clinical evidence has found that it is best utilised for those CNV lesions that are Juxtafoveal. It is known to cause some retinal pigment layer degeneration which if subfoveal can have an impact on quality of vision. Comparative associated risks of all current available technologies and proposed technology should be acknowledged.	Comment noted
	The Royal College of Ophthalmologists	Yes	Comment noted.
	Royal College of Pathologists	Yes	Comment noted.
	Macular Disease Society	We believe Vertepporfin PDT and Bevacizumab to be the only alternative treatments in use.	Comment noted.

Section	Consultees	Comments	Action
Outcomes	Commissioning Support Appraisals Service	Best corrected visual acuity (BCVA) is the primary outcome of the main RCTs indentified. Secondary outcomes included: the proportion of participants showing letter improvements within the BCVA at various cut offs; proportion of patients with active leakage in the eye over time, change in central retinal thickness, change in lesion size and morphology, and total number and time to first retreatment (with ranibizumab).	Comment noted.
	Novartis	Best corrected visual acuity (both eyes) and contrast sensitivity was not measured in the pivotal ranibizumab trials. Best corrected visual acuity (both eyes) is not routinely measured. Although BCVA in the treated eye will capture a critical health related benefit, the absence of measures of other visual function (including contrast sensitivity, visual field, depth perception) means that the full spectrum of visual impairment will not be reflected. Thus, NEI VFQ-25 outcomes will be important in capturing the health related benefits of ranibizumab treatment.	Comment noted. The outcome listed in the scope should be those that are important to patients and/or their carers. Best corrected visual acuity (both eyes) and contrast sensitivity are listed as outcomes in the scope as they are important outcomes for patients.
	Royal National Institute for the Blind	Best corrected visual acuity in the affected eye is a good outcome measure. It is also important to consider improvements in functional vision. For example, does the improvement in vision allow the patient to perform day to day tasks in different places? Clincians tell us that they notice a deterioration in contrast sensitivity in patients with the eye condition. As we do not live in a world with perfect contrast, testing contrast sensitivity will show what the patient's vision will be like in the real world. Therefore, we feel this is a worthy outcome measure. In terms of adverse affects, people with myopia are more likely to suffer retinal detachments following intravitreal injections/surgery. This should be taken into consideration when looking at outcome measures.	Comment noted. Retinal detachments following intravitreal injections/surgery would be captured as an adverse event of treatment and therefore does not need to be listed separately in the scope. Best corrected visual acuity (affected eye) and contrast senility are listed as outcomes in the scope as they are important outcomes for patients.

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	Royal College of Nursing	Yes this a comprehensive list.	Comment noted.
	The Royal College of Ophthalmologists	Also may wish to consider change in VA from baseline	Comment noted.
	Royal College of Pathologists	Yes	Comment noted.
	Macular Disease Society	The outcomes are the most important ones	Comment noted.
Economic analysis	Commissioning Support Appraisals Service	Dosage and frequency is yet to be determined and will depend on marketing authorisation.	Comment noted. The technology will be appraised within its licensed indications.
	Royal National Institute for the Blind	Clinicians tell us that patients may only need two or three injections to treat this condition. This means the overall cost of treatment should be low.	Comment noted. The potential impact on resource costs and savings for the NHS and Personal Social Services that would be expected from the introduction of the technology should be presented in an appraisal.
	The Royal College of Ophthalmologists	No statement on what an appropriate time horizon is	Comment noted. The scope states that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

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	Royal College of Pathologists	This should be life-long and address the challenge of how long patients should be treated for.	Comment noted. The scope states that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
	Macular Disease Society	Myopic CNV occurs in a relatively young population (unlike wet age-related macular degeneration). The economic analysis should take account of the financial impact of sight loss on a person of working age or a person with family/caring responsibilities eg that of caring for young children or elderly relations. The benefits of treating this population may not be reflected in the QALY calculation.	Comment noted. The scope states that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
Equality and Diversity	CSAS	No equality issues were identified.	Comment noted.
	Royal National Institute for the Blind	As mentioned above, the condition is most likely to affect people of working age.	Comment noted.
	The Royal College of Ophthalmologists	No	Response noted.
	Royal College of Pathologists	No equality concerns	Comment noted.

Section	Consultees	Comments	Action
	Macular Disease Society	Absence of NICE guidance on the treatment of myopic CNV has been used by Primary Care Trusts as a reason to refuse treatment to patients with the condition. This leads some patients to turn to the private sector to retain their sight. Poorer patients who are refused treatment cannot do this.	Comment noted. The relevance of equalities issues to the appraisal was discussed at the scoping workshop. The issue raised falls outside the population protected by the equality legislation and it is not expected that an appraisal of ranibizumab will impose any restrictions in terms of the access to treatment for people on low income. Issues of equality are reviewed throughout the appraisal process.
Other considerations	Commissioning Support Appraisals Service	A multiple technology appraisal may be appropriate as bevacizumab and ranibizuab are both used off license for the indication under consideration.	Comment noted. NICE does not have the remit to appraise the use of technologies outside their licensed indications. Therefore an appraisal of bevacizumab for this indication would only happen if the manufacturer of that technology was to seek marketing authorisation for this indication.
	Royal National Institute for the Blind	We would like the remit to consider the treatment of both eyes. Many of the patients we talk to develop the condition in both eyes.	Comment noted. Best corrected visual acuity (both eyes) is an outcome listed in the scope. The draft remit does not exclude the use of the technology in both eyes.

Section	Consultees	Comments	Action
	The Royal College of Ophthalmologists	1. It will be clinically helpful to consider extending the indication to include other non-AMD CNVs (in addition to those that occur secondary to myopia eg CNV associated with angioid streaks and multifocal choroiditis). These other indications are a lot less common than CNV associated with pathologic myopia. 2. It is expected that VEGF-Trap (Eylea, Bayer/Regeneron) may receive its EU Marketing Authorisation before the end of 2012 or early 2013.	Comment noted. The technology will be appraised within its licensed indications. Comment noted. The scoping workshop attendees stated that bevacizumab and verteporfin are routinely used in some centres in England and Wales, and they are therefore appropriate comparators.
	Royal College of Pathologists	Again aging is an issue and it will be important to consider whether or not there are potential side-effects from very long term treatment	Comment noted. The scope states that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
	Macular Disease Society	None	Comment noted.
Questions for consultation	Commissioning Support Appraisals Service	The technology under consideration is an additional treatment option. There is currently only one licensed treatment for this indication (verteporfin photodynamic therapy).	Comment noted.

Section	Consultees	Comments	Action
	Novartis	Although QALYs based on BCVA will capture a critical health related benefit, the absence of measures of other visual function (including for example, contrast sensitivity, visual field, depth perception) in the QALY calculation means that the full spectrum of visual impairment will not be reflected.	Comment noted. If this topic is formally referred to NICE as a technology appraisal, innovation will be considered by the Committee when formulating its recommendations.
	Royal National Institute for the Blind	We consider this technology to be innovative as there is no current treatment in routine use for choroidal neovascularisation associated with pathological myopia. Ranibizumab is likely to result in substantial health-related benefits for patients.	Comment noted. If this topic is formally referred to NICE as a technology appraisal, innovation will be considered by the Committee when formulating its recommendations.
	Royal College of Nursing	Yes, as clinical evidence and research evidence demonstrates a positive outcome. There appears to be a higher incidence of stability of the CNV lesion and recovery of vision levels using less frequent intravitreal injection than that seen in CNV due to ARMD.	Comment noted. If this topic is formally referred to NICE as a technology appraisal, innovation will be considered by the Committee when formulating its recommendations.

Section	Consultees	Comments	Action
	The Royal College of Ophthalmologists	Yes. There is currently only one licensed therapy for CNV secondary to myopia - verteporfin PDT. However, this treatment did not meet its primary endpoint at 24 months, and does not result in recovery of lost vision for the average eye treated for this condition. Multiple lines of evidence support a consistent recovery of vision loss (due to CNV secondary to pathologic myopia) when treated with intravitreal ranibizumab. In addition to the several case series, the interim analysis of the REPAIR Study data provides supporting evidence. The quality of life in these patients is also enhanced by the use of this technology. STA is appropriate	Comment noted. Following discussion at the scoping workshop it was agreed that it was appropriate to seek a formal referral to appraise ranibizumab.
	Royal College of Pathologists	The technology has transformed the management of age-related macular degeneration and could well provide a step-change in the management of pathological myopia. QALY's are certainly used for ophthalmic problems. There are more specific tools for assessing visual impairment but I am not qualified to assess their relative merits.	Comment noted. If this topic is formally referred to NICE as a technology appraisal, innovation will be considered by the Committee when formulating its recommendations.

Section	Consultees	Comments	Action
	Macular Disease Society	Off label anti-VEGF therapy has been in use patchily for some years for the treatment of myopic CNV. Some Primary Care Trusts (PCTs) appear to permit the use of Ranibizumab, others allow the use of Bevacizumab usually via special cases panels. Some PCTs have historically refused to permit any treatment although we believe that many patients do finish up being treated as part of trials. Some hospital trusts appear willing to bear the cost of individual patients' treatment without seeking approval from the local PCT. Our patient advocacy service helps patients make the case for treatment where they have been refused. In our considerable experience post-code lotteries have a profoundly distressing effect on the patients who cannot access treatment. To lose one's sight is terrible but to know that there is a treatment which one cannot have simply because of where one lives in the country makes the loss even worse. Some patients pay privately (usually for Bevacizumab) to maintain their vision but others do not have the financial resources to do so. An effective and universally available treatment for these patients would be a step change in the management of the condition.	Comment noted. If this topic is formally referred to NICE as a technology appraisal, innovation will be considered by the Committee when formulating its recommendations.

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

Comment 3: provisional matrix

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	*Proposal made by:*		*Action taken:* Removed/Added/Not included/Noted	*Justification:*
1..	Add the British Ophthalmic Anaesthesia Society (BOAS) to professional groups	NICE Secretariat		Added	The British Ophthalmic Anaesthesia Society (BOAS) meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a professional group.
2.	Add Eyehope to relevant research groups	NICE Secretariat		Added	Eyehope meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a relevant research group.
3.	Add the Health Research Authority to research groups	NICE Secretariat		Added	The Health Research Authority meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a research group.

3.	Add NHS England to consultee other.	NICE Secretariat		Added	NHS England meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a research group.