NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Clinical Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Clinical Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The 'Specification for manufacturer/sponsor submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Lucentis™(ranibizumab) for the treatment of visual impairment due to diabetic macular oedema (referred to hereafter as DMO).

Following a positive recommendation by NICE for ranibizumab for the treatment of DMO, the patient access scheme (PAS) will be applied to all supplies and preparations of ranibizumab applicable to all current and future indications.

3.2 Please outline the rationale for developing the patient access scheme.

The simple discount PAS is a mechanism through which the NHS will be able to procure ranibizumab at a price [redacted] lower than the current list price. The level of the PAS has been established at a point where ranibizumab is a cost-effective intervention compared to the current standard of care for the treatment of DMO, in an analysis that incorporates the Appraisal Committee's preferred assumptions. The PAS will therefore facilitate patient access to optimal treatment for DMO.

Furthermore Novartis considers that the savings to the NHS, associated with the treatment of patients with wet age-related macular degeneration (wet AMD) generated by the new PAS, will allow a significant number of DMO patients to be treated with ranibizumab.

From a cost-effectiveness perspective, the cost effectiveness of ranibizumab in a DMO population is offset by the cost effectiveness observed in the wet AMD population (1;2). Thus in terms of net monetary benefit (NMB) [1] *to the NHS of implementing ranibizumab treatment across the licensed indications, NMB improves as a result of the proposed PAS.*

[1] NMB = $R_T\Delta E - \Delta C$, where R_T is the willingness to pay threshold, ΔE are the incremental effects and ΔC are the incremental costs. NMB >0 are considered cost effective (3).

Savings in the first full year the PAS is operational

- *The estimated NHS savings associated with ranibizumab used in wet AMD in the first year of the new PAS would be more than [redacted] (Novartis UK, data on file, 2012). These savings are compared to the existing PAS (2).*
- *This [redacted] saving equates to over [redacted] vials of ranibizumab which would allow over [redacted] patient eyes with DMO to receive ranibizumab in their first treatment year (mean of 7 injections). This is equivalent to more than [redacted] patients, assuming 30% of patients with DMO are also treated in the fellow eye in their first treatment year (paragraph 4.21 of (1)).*
- *If the savings delivered from wet AMD treatment are applied to the administration and monitoring visit costs, as well as drug acquisition costs, then a complete ranibizumab service for 1 year can be provided for over [redacted] DMO patients, including bilateral treatment for those that need it. This conservatively assumes that patients requiring treatment in both eyes receive separate treatment and monitoring visits for each eye.*

Longer term savings

- *Over 3 years, the new PAS equates to estimated NHS savings of more than [redacted] in wet AMD alone (Novartis UK, data on file, 2012). This saving is equivalent to [redacted] ranibizumab vials.*
- *The RESTORE extension study has now completed and confirms that vision is sustained over 3 years, with a reducing number of injections in a monotherapy regimen (Table 1). Assuming the treatment frequency observed in the RESTORE core and extension study in years 1, 2 and 3, [redacted] vials is equivalent to the treatment of over [redacted] eyes for 3 years ([redacted] patients, if 30% require second eye treatment).*

Table 1: RESTORE injection frequency declines over time with sustained BCVA, ranibizumab 0.5 mg monotherapy

	Year 1 (core study assessment)	Year 2 (interim analysis, extension study)	Year 3 (final analysis, extension study)	Total injections over 3 years
Mean number of injections	7.0	3.9	2.9	13.8
Percentage of patients with zero injections	n/a[1]	19.3%		-
Mean change in BCVA from baseline	+6.8	+7.9	+8.0	-

SOURCE: (4;5) 1. By protocol, all patients in the ranibizumab treatment arms received ranibizumab during the first 3 months of RESTORE.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

Financially-based scheme: simple discount to list price.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

Following positive NICE guidance for ranibizumab in DMO, the PAS will apply to all supplies and preparations of ranibizumab applicable to all current and future indications. Thus, the significant savings to the NHS realised from lower drug costs in wet AMD will allow more than the predicted number of DMO patients to be treated with ranibizumab (section 3.2).

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example,

degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The PAS will apply when patients commence treatment. It is not dependent on any criteria.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

All patients prescribed ranibizumab will meet the PAS criteria.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The NHS Trust signs a commercial agreement with Novartis Pharmaceuticals UK Ltd as per the standard NHS pharmacy procurement procedure. The hospital pharmacy then orders ranibizumab through the normal procedure. Ranibizumab is provided to the NHS Trust at list price minus the PAS discount, applied to the invoice. The amount of discount will remain commercial in confidence.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

No additional information, further to the standard NHS pharmacy procurement procedure, need be collected routinely.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

3.10 Please provide details of the duration of the scheme.

The PAS will be in place until NICE review of guidance for the treatment of visual impairment due to DMO, and subject to Department of Health agreement.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

A draft purchase agreement letter and terms are included as an appendix.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

Following positive NICE guidance for ranibizumab in DMO, the PAS will apply to all supplies and preparation of ranibizumab applicable to all current and future indications.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Updates to the economic model are described in section 4.3 below.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The simple discount is applied as a change to the unit cost of a ranibizumab injection in the model (worksheet 'appendix 1', cell B6).

The TAG does not describe one most plausible scenario or one ICER considered reflecting all of the Committee's preferred assumptions. At paragraph 4.29 of Technology Appraisal Guidance 237 (the TAG; (1)), it is noted that 'the Committee believed that the manufacturer's revised basecase model still provided an inaccurate

reflection of likely clinical practice in at least six respects'. Each of these concerns is set out below, with a description of changes to the model to reflect the assumption that the Appraisal Committee considered most plausible. These assumptions and the revised basecase are summarised in Table 2*. We highlight that, to meet the requirement of the NICE process, new evidence has not been incorporated into the model and the analysis has been adapted only to address the concerns of the Committee in the manner described in the TAG. Thus, we acknowledge that there are limitations to the approaches used in the basecase.*

Table 2: Summary of the Committee's six concerns and revisions to the basecase

Concern	Basecase assumption
Not accounting for the need to treat both eyes in a large proportion of people with diabetic macular oedema	The BSE ICER is increased by a factor of 1.5
Using a range of utilities that was broader than would be expected according to the assumptions of the model	The 'Brazier utilities', as published by Csozky-Murray and colleagues, are used in the basecase to reflect treatment of the BSE
Underestimating the amount of ranibizumab that people with diabetic macular oedema are likely to need	The basecase includes 14 injections over 3 treatment years based on available evidence (Table 1). A threshold analysis approach is used to inform the potential impact of injections in subsequent years.
Overestimating the residual benefit associated with ranibizumab projected beyond the treatment phase	The time horizon has been curtailed to 10 years, to reduce uncertainty around the extrapolation of benefit. A threshold analysis testing an alternative assumption of residual benefit has been presented.
Applying unequal assumptions about treatment visits and monitoring visits for people treated with ranibizumab and those treated with laser photocoagulation	The assumptions are equal in the basecase.
Overestimating the degree of glycaemic control that would be expected in people treated in clinical practice, and thus over-estimating ranibizumab cost effectiveness	The exploratory nature of the HbA1c subgroup cost effectiveness analysis is not appropriate for a basecase analysis.

a. *Not accounting for the need to treat both eyes in a large proportion of people with diabetic macular oedema*

- *At section 4.21 of the TAG, the Committee noted its preference for a scenario that simulated treatment in both eyes. This scenario was noted to result in an ICER approximately 50% higher than the basecase.*

- *It is noted elsewhere in the TAG that the manufacturer's assumption of a 25% uplift in incremental QALY gain for the worse-seeing eye did not appear to be evidence-based (section 3.41).*
- *The Committee notes further at section 4.24, that the TA155 Committee multiplied the ICERs generated by the better-seeing eye (BSE) model by a factor of 1.5, equivalent to an increase in the ICER of 50%, in order to approximate the lesser QALY gain from improving BCVA in a worse-seeing eye (WSE) and the increased costs of treatment for those patients requiring treatment in both eyes. It is noted that the two approaches have broadly the same impact on the ICER.*

Considering together these elements of the TAG, the Committee's preferred approach is taken to be to increase a BSE ICER by a factor of 1.5 to approximate the cost effectiveness of treating both eyes. Increasing a BSE ICER by 1.5 is consistent with existing NICE guidance applied to a wet AMD population requiring treatment in both eyes in some cases.

Thus, in the base case an ICER for treatment of both eyes is approximated by multiplying the BSE ICER by 1.5.

b. ***Using a range of utilities that was broader than would be expected according to the assumptions of the model***

At paragraph 4.23 the Committee noted its preference for the RESTORE EQ-5D utility values in an extended regression analysis, reflecting the influence of diabetic comorbidities on health-related quality of life, over the original RESTORE EQ-5D utility values presented by Novartis. However, whilst the Committee considered these to be closer to the range invariably seen for a WSE, they were noted to be considered 'surprisingly large'. As noted in the TAG, the RESTORE EQ-5D utility values are associated to BCVA of predominantly, although not exclusively, the WSE as this was, by protocol, the treated eye of the majority of patients in RESTORE.

Given the reservations expressed repeatedly by the Committee regarding the face validity of the RESTORE utilities and the well accepted limitations of the EQ-5D

instrument in eliciting utility values associated to visual impairment (described in response to the ACD; section 5 , and acknowledged as having been taken into account by the Committee at the ranibizumab in DMO appeal hearing), we conclude that the RESTORE EQ-5D data are not considered by the Committee to be the most plausible for inclusion in the basecase. Moreover, taking account of the Committee's preferred approach to approximate cost effectiveness of treatment of both eyes where this is needed (discussed above), utility values associated to BCVA in a BSE are required.

In response to the ACD, Novartis submitted cost-effectiveness scenarios including the alternative utility values derived by Brazier and colleagues, and Lloyd and colleagues (6;7). The 'Brazier utilities', using the equation published by Czosky-Murray and colleagues (appendix 6.1; (8)), have been considered to be preferred by the Committee over the 'Lloyd utilities' for use in the basecase because:

- *The study elicited utilities using the time trade-off technique in members of the UK general public patients who were fitted with contact lenses to simulate varying degrees of visual impairment, thus meeting the NICE reference case but avoiding the limitations of the EQ-5D in generating utility values appropriate to visual impairment due to retinal disease (9;10). The Lloyd utilities were elicited using EQ-5D.*
- *The 'Brazier utility' values avoid potential confounding of the relationship between BCVA and utility by diabetic comorbidities, raised by the Committee as a concern (section 3.28 of the FAD).The Lloyd utilities were elicited for health state descriptions (vignettes) describing the impact of visual impairment due to diabetic retinopathy, and also diabetic neuropathy and nephropathy.*
- *During the appraisals of ranibizumab for wet AMD and RVO, the two Committees both expressed a preference for the 'Brazier utilities' over others derived from utility instruments which may not fully capture the impact of visual impairment on the patient's quality of life (2) or adjust for age (11).*

The 'Lloyd utilities' are applied in scenario analyses in Table 10. In the interests of transparency, Table 10 also presents a 'treated eye' analysis simulating treatment of one eye, but incorporating the RESTORE utilities. We acknowledge the Committee does not consider a treated eye analysis to reflect clinical practice. However, to increase by 1.5 an ICER generated using the trial-based (RESTORE) utilities would not be consistent with previous approaches nor our interpretation of the Committee's preferred assumptions, given that these utilities are associated to BCVA in predominantly the WSE.

c. Underestimating the amount of ranibizumab that people with diabetic macular oedema are likely to need

The Committee describes at paragraph 4.25, its concern that the model underestimates the number of ranibizumab injections in a monotherapy regimen because i) the number of injections in year 2 are based on the DRCR.net ranibizumab plus deferred laser arm ii) there is no evidence to support an assumption that the number of injections declines in year 3 and 4 iii) it may be unrealistic to assume that treatment would not continue beyond 4 years.

There is growing evidence that treatment with ranibizumab reduces over time whilst the improvement in BCVA is sustained (Table 1). However, evidence remains limited for the frequency of treatment beyond 3 years. Therefore a threshold analysis approach has been employed to assess the maximum number of injections per patient that could be administered whilst keeping the ICER below £30,000 per QALY. In the model, the number of injections is increased in year 3 to simulate continued treatment. Thus, the associated benefit (stable BCVA) of further treatment is not captured as BCVA and ranibizumab cost effectiveness may be underestimated.

d. Overestimating the residual benefit associated with ranibizumab projected beyond the treatment phase

A 10 year time horizon is used in the basecase to limit the uncertainty of extrapolating continued ranibizumab benefit. This has been reduced from the original 15 year time horizon in response to the Committee's comments in the TAG at paragraph 4.26 (1). This may be a conservative approach, especially when

considered alongside the threshold analysis of increased injections for additional treatment years.

Scenario analyses applying alternative time horizons are presented *in Table 10.* A threshold analysis is presented in appendix 6.2 where the average BCVA deteriorates more quickly in ranibizumab-treated patients than in laser-treated patients.

e. *Applying unequal assumptions about treatment visits and monitoring visits for people treated with ranibizumab and those treated with laser photocoagulation*

Novartis maintains that laser is predominantly delivered in a 'two-stop' clinic arrangement where patients assessed as requiring laser are brought back to a separate laser clinic. Conversely, ranibizumab is predominantly provided in a 'one-stop' or 'see & treat' clinic. The difference arises due to the longer average time, and more variation in time, needed to administer laser than an intravitreal injection: A separate laser clinic avoids longer waiting times that could arise in a 'see & treat' laser clinic. Thus, assuming that a visit for treatment with ranibizumab would double as a monitoring visit, but not assuming the same for laser photocoagulation is unequal yet appropriate and consistent with clinical practice.

Nonetheless, we acknowledge there is likely to be variation between centres and without definitive survey evidence across the NHS to persuade the Committee of an alternative assumption. Therefore, we present as a basecase the assumption that treatment visits for both laser and ranibizumab double as a monitoring visits (Table 3). The total number of visits, as presented in Table 3 is now consistent with advice of the clinical specialists to the Committee outlined in paragraph 4.4 of the TAG (1). Alternative assumptions are included in sensitivity analyses presented in section 4.11.

Table 3: Frequency of treatment and monitoring visits (base case)

	Year 1		**Year 2**		**Year 3**		**Years 4 +**	
	Ranibizumab	**Laser**	**Ranibizumab**	**Laser**	**Ranibizumab**	**Laser**	**Ranibizumab**	**Laser**
Treatment visit	7	2	4	1	3	1	0	0
Monitoring visit	5	2	4	3	3	3	2	2
Total visits	**12**	**4**	**8**	**4**	**6**	**4**	**2**	**2**

SOURCE: (1;12)

f. Overestimating the degree of glycaemic control that would be expected in people treated in clinical practice, and thus over-estimating ranibizumab cost effectiveness

We draw attention to the clinical and cost effectiveness data for the HbA1c subgroups (Table B9 and table B61 of the original submission). In the RESTORE study, the subgroup HbA1c ≥8% is comprised of 28 and 30 patients in the laser and ranibizumab 0.5mg arms, respectively. As noted in the original submission, the cost effectiveness analysis across subgroups presented at that time requires cautious interpretation due to small sample sizes in some cases, resulting in a very small number of patients in extreme health states driving the results (section 6.9.4 of original submission). As can be observed in the executable model, the probability of an improvement or deterioration in BCVA in year 1 is frequently determined by one patient observation (worksheet 'Library of Transition Matrices' cells E48: AJ93).

In light of the consideration of the Committee that the cost effectiveness findings across HbA1c subgroups were exploratory (paragraph 4.28), we do not consider modelling of a population with poorer glycaemic control to reflect the Committee's view of the most plausible scenario for ranibizumab.

Additional issue: Subgroup of patients with thicker, more oedematous retina

In addition to the six issues that the Committee identified with regards to the basecase analysis, at paragraph 4.32 and 4.33 of the TAG, the Committee sets out its concerns with respect to the cost effectiveness analysis of ranibizumab treatment for patients with thicker retina. For completeness, Novartis has tried to address these concerns in appendix 6.2.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The cost effectiveness model uses the proportion of patients with at least 10 letter improvement and deterioration in BCVA. This is unchanged from the original

submission. These outcomes at 12 months are presented in Table 4. The 3-monthly transition probabilities derived from patient level data are available in the executable model at worksheet 'Library of transition matrices', cells AL1:BQ46 for the basecase. Given the requirements of the rapid review process, additional effectiveness data has not been updated in the executable model. However, the assumption of stability in treatment years 2 and 3 is noted to be broadly the same as that observed in the RESTORE extension study (Table 1).

Table 4: Proportion of patients with ≥10 letters change in BCVA from baseline, at M12

	Ranibizumab 0.5 mg	Laser
Proportion of patients with at least 10 letter improvement	37.4%	15.5%
Proportion of patients with at least 10 letter deterioration	3.5%	13.7%

SOURCE: (4)

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'

Not applicable: There are no costs associated with the implementation and operation of the PAS.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Not applicable: There are no costs associated with the implementation and operation of the PAS.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below.

*The revised basecase analysis, incorporating the Committee's preferred assumptions and the revised PAS, suggests that ranibizumab is cost effective around the £20,000 per QALY threshold (*Table 7*).*

This analysis includes a mean of 14 injections over 3 treatment years, and adjusts for the need to treat a large proportion of patients in the fellow eye.

In the event that some patients require continued treatment to maintain stable vision beyond three years, then the threshold analysis demonstrates that a mean of 18 injections can be delivered over 10 years under a £30,000 per QALY threshold. This is equivalent to 4 injections in years 4 to 10. It is noted that a laser maintenance approach beyond initial ranibizumab treatment was rejected by the Committee as defined in the original submission and basecase. However, we note expert clinical opinion that it is likely that laser will remain part of the DMO treatment paradigm for many patients, alongside pharmacotherapeutic options (paragraph 4.4 of the TAG). Thus, Novartis believes that a mean of 4 injections per patient over 7 years should be considered in this context.

Table 5: Basecase cost-effectiveness results, list price

	Laser	**Ranibizumab**
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)		[redacted]
QALYs	[redacted]	[redacted]
QALY difference		[redacted]
BSE ICER (£)		23,730
Bilateral ICER (£)		**35,595**

Table 6: Basecase cost-effectiveness results, without revised PAS

	Laser	Ranibizumab
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)		[redacted]
QALYs	[redacted]	[redacted]
QALY difference		[redacted]
BSE ICER (£)		20,132
Bilateral ICER (£)		**30,198**

Table 7: Basecase cost-effectiveness results, with revised PAS

	Laser	Ranibizumab
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)		[redacted]
QALYs	[redacted]	[redacted]
QALY difference		[redacted]
BSE ICER (£)		14,137
Bilateral ICER (£)		**21,205**
Mean number of injections per patient maintaining ICER <£30k per QALY		**19.5**

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

Table 8: Basecase incremental results, without revised PAS

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs) [BSE]	ICER (£) incremental (QALYs) [BSE]	Bilateral ICER (£)
Laser	[redacted]	7.58	[redacted]					
Ranibizumab	[redacted]	7.58	[redacted]	[redacted]	[redacted]	20,132	20,132	**30,198**

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 9: Basecase incremental results, with revised PAS

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs) [BSE]	ICER (£) incremental (QALYs) [BSE]	Bilateral ICER (£)	Maximum number of injections per patient <£30k per QALY
Laser	[redacted]	7.58	[redacted]						
Ranibizumab	[redacted]	7.58	[redacted]	[redacted]	[redacted]	14,137	14,137	**21,205**	**19.5**

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Table 10: Results of deterministic sensitivity analysis and scenario analysis, with and without revised PAS

	Incremental costs (£) (without revised PAS)	Incremental costs (£) (with revised PAS)	Incremental QALYs	Bilateral ICER (£) (without revised PAS)	Bilateral ICER (£) (with revised PAS)	Maximum number of injections per patient <£30k per QALY[1] (without PAS/with PAS)
Base case	[redacted]	[redacted]	[redacted]	**30,198**	**21,205**	**-/19.5**
Discount rate 0% for costs and QALYs	[redacted]	[redacted]	[redacted]	25,963	17,951	15.5/22
Discount rate 6% for costs and QALYs	[redacted]	[redacted]	[redacted]	33,233	23,535	-/17.5
Discount rate 3.5% for costs and 0% for QALYs	[redacted]	[redacted]	[redacted]	26,266	18,680	15.5/22.5
Time horizon 20 yrs	[redacted]	[redacted]	[redacted]	19,541	12,803	20/28.5
Time horizon 15 yrs	[redacted]	[redacted]	[redacted]	22,415	15,102	18/25.5
Time horizon 5 yrs	[redacted]	[redacted]	[redacted]	56,698	41,568	-/-
Time horizon 1 yr	[redacted]	[redacted]	[redacted]	177,625	134,454	-/-
Long term progression: stable BCVA	[redacted]	[redacted]	[redacted]	30,462	21,505	-/19
Stopping rule in year 1[2]	[redacted]	[redacted]	[redacted]	25,468	17,811	16/21.5
Lloyd utility values unadjusted[3,4]	[redacted]	[redacted]	[redacted]	36,759	25,911	-/16
Lloyd utility values, adjusted[3]	[redacted]	[redacted]	[redacted]	62,257	43,716	-/-
Relative risk of mortality = 2.0[5]	[redacted]	[redacted]	[redacted]	29,459	20,636	-/20
Day care setting in 25% treatment visits	[redacted]	[redacted]	[redacted]	36,233	27,240	-/15
Cost of blindness +25%	[redacted]	[redacted]	[redacted]	28,398	19,404	-/20.5
Cost of blindness -25%	[redacted]	[redacted]	[redacted]	31,999	23,006	-/18
6 total visits in year 2	[redacted]	[redacted]	[redacted]	29,369	20,376	-/20
12 total visits in year 2	[redacted]	[redacted]	[redacted]	31,897	22,863	-/18.5
Monitoring doubles as treatment visit for ranibizumab only[4]	[redacted]	[redacted]	[redacted]	28,452	19,459	14.5/20.5
Monitoring doubles as treatment visit for neither ranibizumab and laser[4]	[redacted]	[redacted]	[redacted]	34,560	25,566	-/16
No adverse events	[redacted]	[redacted]	[redacted]	30,345	21,351	-/19
Treated eye analysis, using trial based utilities[4, 6]	[redacted]	[redacted]	[redacted]	54,856	38,519	-/-

1. Sensitivity analysis around injection frequency replaced with threshold analyses
2. Stopping rule introduced based on the original submission (no treatment at >75 letters in year 1)
3. The Lloyd utility values as reported have a 'dip' in utility at moderate visual impairment, which was adjusted for in the sensitivity analysis presented to NICE originally to give a smooth curve and in order to be conservative against ranibizumab (7)
4. Additional analyses to original submission
5. Based on ERG comments to Novartis ACD response
6. This analysis applies the adjusted RESTORE utilities, and by definition includes predominantly WSEs. Only one eye is assumed to be treated.

With the revised PAS, the cost effectiveness of ranibizumab is observed to remain below £25,000 per QALY in the majority of sensitivity and scenario analyses (Table 10). As expected, given that treatment costs are accrued in years 1 to 4 and benefits later in the time horizon, time horizons of 1 and 5 years generate higher ICERs.

The ERG has acknowledged that ranibizumab injections are delivered predominantly in an outpatient scenario, thus sensitivity analysis around treatment setting is less relevant. It is important to note that the model costs have not been updated from the NHS Reference Costs 2008/09 used in the original submission in 2010, for consistency across the appraisal. However, recent NHS Reference Costs to 2010/11 and updates to the cost of blindness suggest that the basecase ICER could be a conservative estimate of cost effectiveness.

With respect to the source of utility values, as expected cost effectiveness analysis of the treatment of predominantly, although not exclusively, the worse-seeing eye using the trial-based EQ-5D utilities produces ICERs above a £30,000 per QALY threshold. Similarly, as does applying the utility values published by Lloyd and colleagues, but adjusted for potential inconsistencies in the data. As described in section 4.3, these analyses are limited by the inclusion of EQ-5D utilities which are may not fully capture the impact of visual impairment on patients' health status.

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

The implementation of a 1.5 increase is made to the BSE ICER to approximate the cost effectiveness of bilateral treatment for those people who need it. This is not a probabilistic input to the model and does not influence individually the denominator and numerator of the ICER. Thus, the probabilistic sensitivity analyses (PSA) will reflect the uncertainty of the BSE ICER. Furthermore, given the threshold analysis approach to quantify injection frequencies that retain the ICER below £30,000 per QALY, probabilistic sensitivity analysis around the basecase ICER is less meaningful.

PSA results have therefore not been presented here, but can be provided for the BSE analysis on request[3].

4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

No further scenarios to those presented in section 4.9 above were described for the main Novartis submission. In appendix 6.4 below, the sensitivity and scenario analyses are repeated assuming that the basecase utilities are the Lloyd utilities. In appendix 6.3, a threshold analysis for continued benefit beyond treatment is presented.

4.12 If any of the criteria on which the patient access scheme depends are clinical variables (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable: the PAS is a simple discount to list price.

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

[3] Therefore in the executable model, distributions for PSA have not been updated.

These are presented in section 4.7, 4.8 and 4.9. All ICERs presented in this document reflect the scenario with the assumptions that the Appraisal Committee considered to be most plausible (described in section 4.3 above). Further sensitivity analyses and scenario analyses are presented in appendices 6.3 and 6.4.

Appendices

5 Appendix A: Additional documents

5.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Refer to associated file Lucentis Net Price Agreement Feb 2011 [version].pdf.

6 Appendix B: Additional evidence

6.1 Calculation for conversion of Brazier utilities (Czoski-Murray 2009) to model health states

Since TA155, the 'Brazier utilities' have been published by Czoski-Murray et al. alongside a linear (ordinary least squares) regression model that estimates the relationship between VA and health state utilities, with an adjustment for patient age (8). Thus, it is possible to derive Brazier utilities for each of the eight BCVA health states in the DMO cost effectiveness model in a similar way to that employed by the TA155 Assessment Group, and including an age adjustment. The alternative utility values applied to the health states of the model using each approach are presented in Table 11. For this calculation, the upper and lower ETDRS letter scores in each health state were averaged to estimate the utility level applicable to each health state, after transformation from the logMAR scale. This ensures that utilities based on the regression equation apply specifically to each health state.

Table 11: Utilities from Czoski-Murray et al calculated for the model health states (mean age of 65)(8)

ETDRS (approximate Snellen equivalent)	logMAR equivalent: lower BCVA	logMAR equivalent: higher BCVA	Utility: lower BCVA	Utility: higher BCVA	Mean utility for health state
86-100 (20/16-20/10)	-0.1	-0.3	0.832	0.905	**0.869**
76-85 (20/32-20/20)	0.2	0	0.721	0.795	**0.758**
66-75 (20/64-20/40)	0.5	0.3	0.611	0.685	**0.648**
56-65 (20/80-20/50)	0.6	0.4	0.574	0.648	**0.611**
46-55 (20/125-20/80)	0.8	0.6	0.501	0.574	**0.537**
36-45 (20/200-20/125)	1	0.8	0.427	0.501	**0.464**
26-35 (20/320-20/200)	1.2	1	0.353	0.427	**0.390**
<25 (<20/320)	1.2	n/a	0.353	n/a	**0.353**

6.2 Threshold analysis for duration of benefit beyond ranibizumab treatment

This analysis has been generated in response to the Committee's concern that it was unrealistic to assume that the relative improvement in vision achieved during the ranibizumab treatment period would persist for the duration of the model (paragraph 4.26 of the TAG). There is no evidence on which to base alternative assumptions of the duration of ranibizumab benefit after treatment cessation. Therefore, the objective of this analysis was to find the highest rate of worsening vision in the ranibizumab treatment arm that would result in an ICER at the £30,000 per QALY threshold.

The analysis increases the probability of worsening BCVA and decreases the probability of BCVA remaining stable in the ranibizumab arm compared to the base case assumptions. The assumptions in the laser arm remain as in the base case. This simulates the convergence of the average BCVA over time in the laser and ranibizumab-treated patients. The transition probabilities in cells CS31:CZ38 and CS44:CZ51 of worksheet 'ranibizumab trial data' were varied until the ICER reached £30,000. A graph illustrating the average BCVA over time in a scenario producing an ICER of £29,793 is presented in Figure 1, with the corresponding probabilities presented in Table 12. The corresponding graph for the base case assumptions is shown in Figure 2*.*

It is observed that, at the £30,000 per QALY threshold, the rate of deterioration in BCVA for ranibizumab-treated patients would need to be more than 1.5 times higher than that of laser-treated patients. The average BCVA of patients in the ranibizumab arm is equal to that of patients in the laser arm when the model cohort at year 10 of the model. There is no clinical evidence to support this rate of worsening for ranibizumab in VEGF-mediated retinal diseases. We suggest that a rate this extreme is unlikely to be observed in clinical practice for the following reasons:

- *As highlighted to the Committee by the clinical experts at paragraph 4.4 and 4.10 of the TAG, there is an expectation that laser would continue to be part of the treatment regimen for patients with DMO, alongside ranibizumab (1). As outlined in the original Novartis submission, the assumption of maintained*

treatment benefit throughout the time horizon was supported by an assumption that patients would continue to receive laser, as required, in order to maintain that the BCVA improvements achieved from ranibizumab treatment (13).

- *In year 2 of the DRCRnet protocol I study, it is observed that the ranibizumab + deferred laser arm and the ranibizumab monotherapy arms begin to diverge during treatment year 2, perhaps suggesting a more beneficial effect of laser applied sequentially to ranibizumab. This may result from thinned retina through early ranibizumab treatment enabling superior uptake of laser treatment and thus a greater beneficial effect. The outcomes of the DRCRnet protocol I study were presented in table B10 and figure 8 in the original submission (13).*

- *In the RESTORE extension, it was observed that almost 20% of ranibizumab treated patients did not require any further injections beyond year 1, yet the average BCVA of the ranibizumab-treated cohort was maintained (Table 1).*

- *The rate of deterioration of BCVA in patients treated with laser alone is also uncertain, as outlined in the Novartis original submission (13). The rate assumed for deterioration of BCVA in the laser-treated arm may be conservative as it does not take into account the impact on BCVA of longer-term damage, such as scar expansion leading to blind spot enlargement.*

Table 12: Probability of change, long term progression in BCVA

	Year 4 and beyond	
	Ranibizumab	**Laser**
Base case		
Worsening	0.025	0.025
No change	0.940	0.940
Improving	0.035	0.035
Threshold analysis		
Worsening	**0.025**	0.025
No change	**0.920**	0.940
Improving	**0.055**	0.035

Figure 1: Average BCVA over time (modelled), threshold analysis

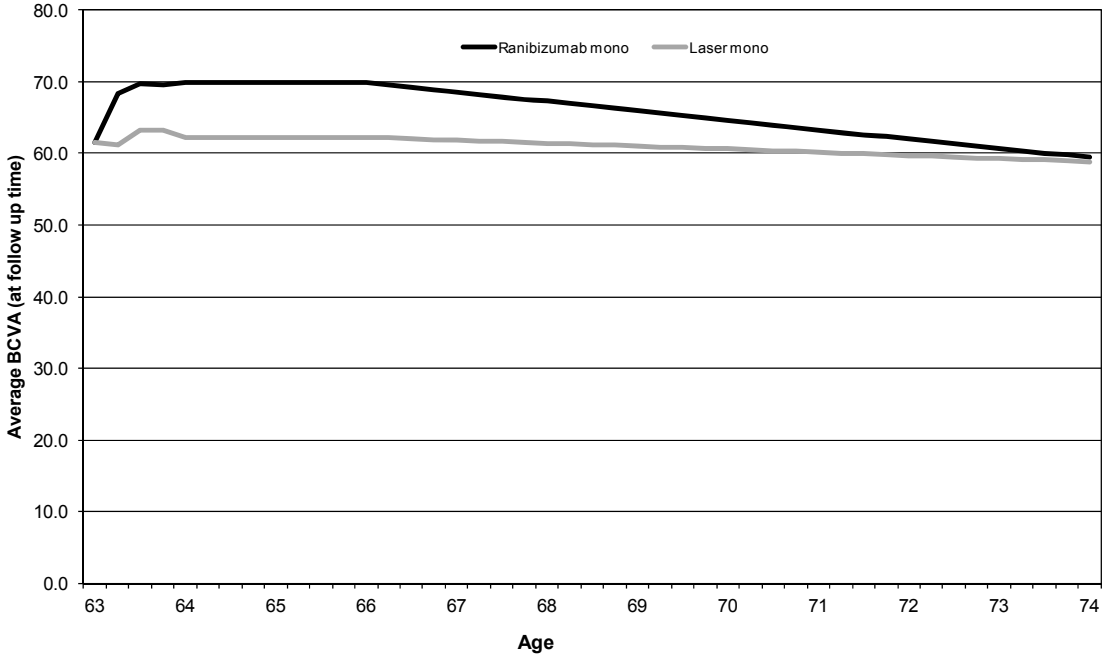
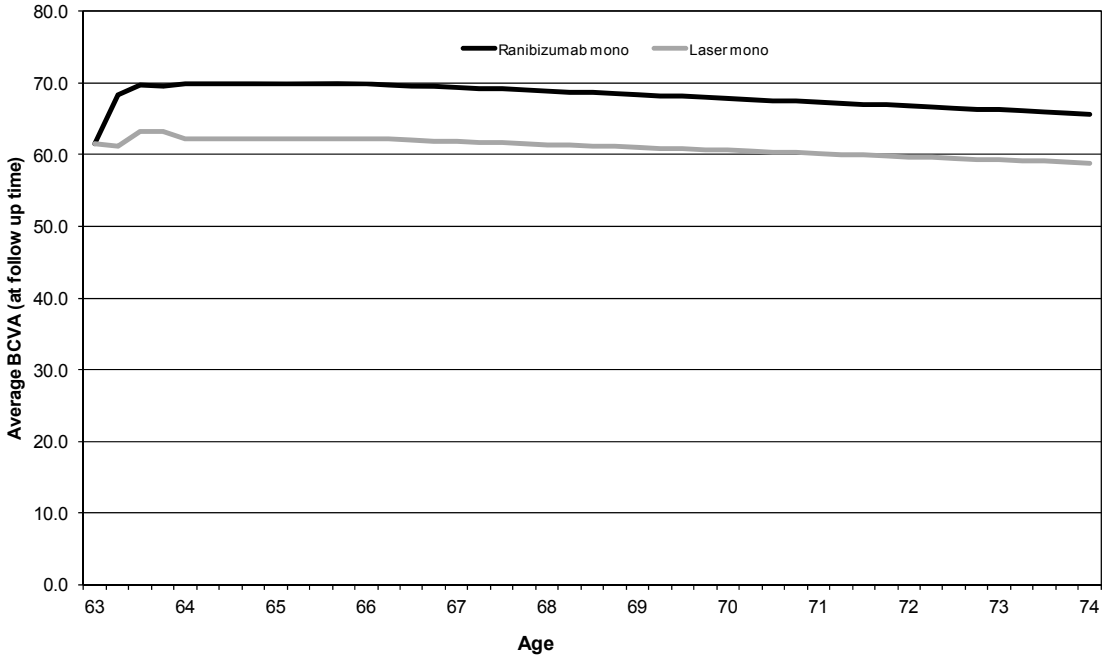


Figure 2: Average BCVA over time (modelled), base case



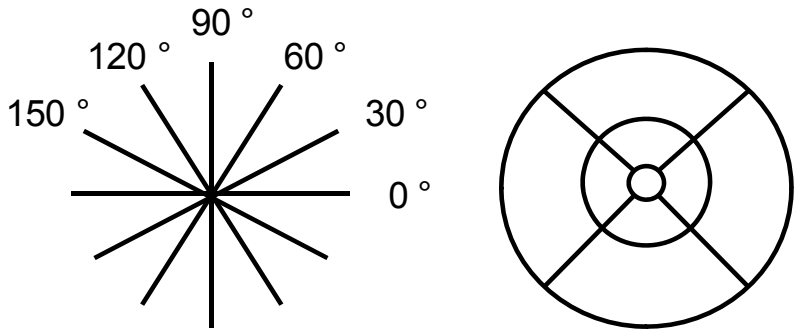
6.3 Subgroup of patients with thicker, more oedematous retina

At paragraph 4.32 and 4.33, the TAG notes the Committee's concern about this subgroup, noting their '...caution about the validity of a biologically mediated subgroup effect, especially given the limited sample sizes from which the model generated its subgroup results....'. For completeness, Novartis has tried to address the Committee's concerns regarding the cost effectiveness analysis in this subgroup below.

Table B9 (appendix 9) of the original Novartis submission presents the primary outcome for the subgroups based on CRT (Central Retinal Thickness). In the Novartis additional analysis (table 12), the primary outcome for the subgroups based on CFT (Central Foveal Thickness) is summarised. A definition of the two alternate measures is summarised below, and illustrated in Figure 3*.*

> ***CFT** is the average of 6 thickness values at the point of intersection of 6 radial scans. That is, it is the average of 6 single point measures of thickness at a single point on the retina. CFT shows considerable variation between visits due to the fact that it is difficult to ensure consistent centration of the scan on the retina from one visit to another; as a result, the position of the intersection point may move from an area with oedema to one without. CFT is synonymous with the term 'centre point thickness' (14).*
>
> ***CRT** is the average thickness across the central 1 mm diameter circular area of the retina (the central subfield), and consists of the average of at least 128 thickness measurements taken from throughout that circular area. It therefore involves repeated measures across a broader area of the retina and is therefore preferred over CFT due to the fact that decentration does not have the potential to skew the results to the extent that CFT does. CRT provides a more reliable measure of retinal thickness. This preference is well recognised (14). CRT is synonymous with the term 'central subfield thickness' (14-16).*

Figure 3: Illustration of the alternative measures of retinal thickness
LEFT: The point of intersection of six radial scans are averaged to derive central foveal thickness (CFT)
RIGHT: The innermost circle represents the 1mm diameter area within which points are averaged to derive central retinal thickness (CRT)



The results of the RESTORE primary endpoint according to both CFT and CRT are presented in Figure 4 *and* Figure 5*. It is observed that patients with thicker retina (>400 μm) lose vision, on average, despite treatment with laser. The difference in treatment effect between laser and ranibizumab-treated patients is statistically significant (p <0.0001). This finding is consistent regardless of whether the CFT or CRT definition is used.*

As highlighted by the clinical specialists to the Committee (paragraph 4.3 of the ACD), the poor laser outcomes for patients with thicker retina is consistent with clinical experience. Supporting evidence from the literature for the baseline risk of vision loss in patients with thicker retina is extremely limited because the introduction of OCT occurred only in the mid 2000s, and wide scale usage only in the late 2000s, which post-dates the majority of the laser studies in DMO.

By either the CFT or CRT measurement, it is also clear from Figure 4 and Figure 5 that the efficacy of laser is higher in patients with retinal thickness between 300 and 400 μm than in either of the other groups. The difference across the groups is more marked when thickness is measured at the centre point (CFT), than when using the preferred CRT measure, resulting in the trend in cost effectiveness across the subgroups that the ERG concluded was erratic (TAG paragraph 3.44). Using the more reliable CRT measure, the trend across subgroups is consistent: the difference in treatment effect in each subgroup increases with increasing retinal thickness.

It is noted that BCVA at baseline in the 300-400 µm group is around 70 letters. Treatment response is likely to be related to BCVA at baseline as well as retinal thickness, and the relatively high BCVA in the 300-400 µm group is likely to contribute to the greater laser efficacy observed in this group. As expected, BCVA at baseline is lowest in the >400 µm group, where patients have the greatest need for treatment.

Figure 4: Average mean change in BCVA from baseline to M1-12, by Central Retinal Thickness (CRT) at baseline

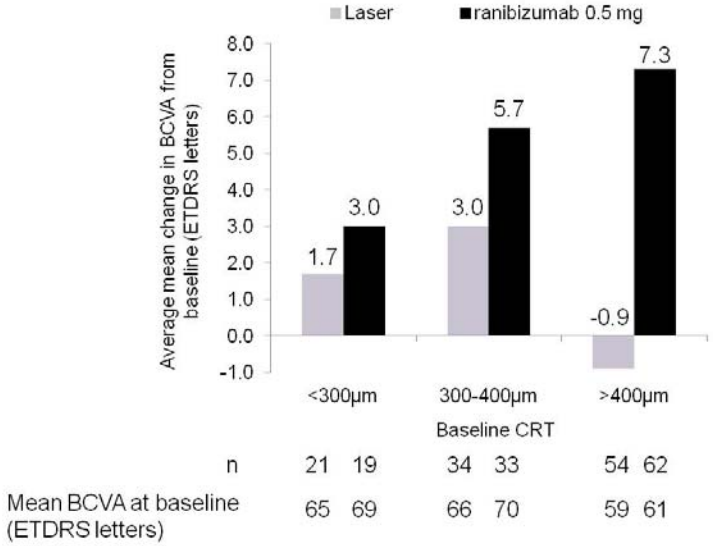
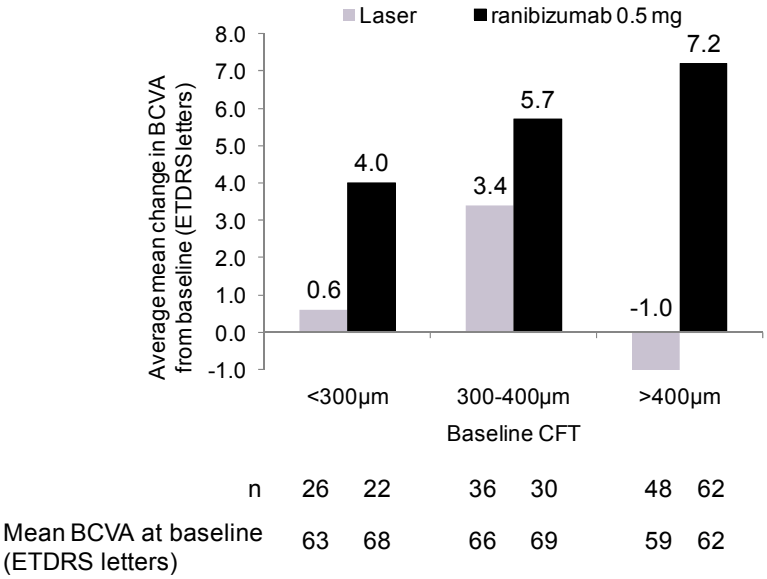
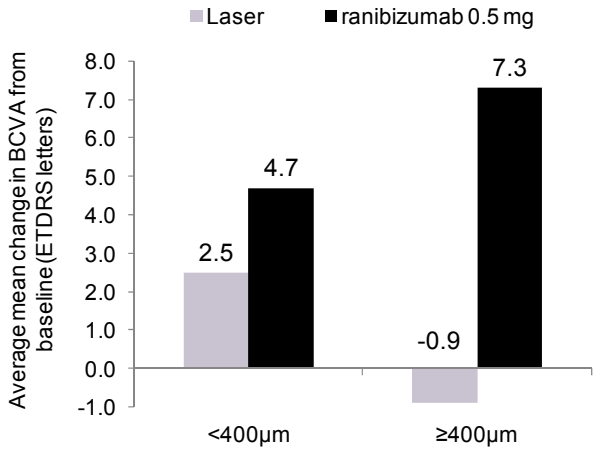


Figure 5: Average mean change in BCVA from baseline to M1-12, by Central Foveal Thickness (CFT) at baseline



As acknowledged by Novartis, the ERG and the Committee, where transition probabilities in the cost effectiveness model are driven by small sample sizes small numbers of patients in extreme health states can have a great impact on the ICER. To lessen the impact of small sample sizes in the model and to obtain subgroups of comparable sizes, the two subgroups with lower values (<400 µm) can be pooled. This avoids the arbitrary definition of the groups noted by the Committee (paragraph 42 of the decision of the appeal panel) and focuses the decision on the group of interest (patients with >400 µm CRT compared to patients with <400 µm CRT). Given the split between patients with <300 and 300-400 um has no meaning in terms of clinical relevance or operationalisability of the subgroup, the categorisation of patients into those with thick retina (>400µm) and those without (<400µm) is more appropriate (Figure 6). Furthermore, it is recognised within the prescribing information that, based on current evidence, patients with >73 letters BCVA at baseline and <300 µm CRT are less likely to benefit from ranibizumab therapy; these patients are unlikely to be prioritised for treatment. The test of treatment-baseline CRT interaction in the ><400 µm group is statistically significant (p <0.01), suggesting that laser works less well in patients with thicker retina. However we recognise the limitations of post-hoc statistical testing.

Figure 6: Average mean change in BCVA from baseline to M1-12, by CRT at baseline



n	55	52	54	62
Mean BCVA at baseline (ETDRS letters)	66	69	59	61

Table 13: Proportion of patients with ≥10 letters change in BCVA from baseline, at M12

	Ranibizumab 0.5 mg	Laser
Proportion of patients with at least 10 letter improvement		
Full RESTORE population	37.4%	15.5%
CRT < 400µm	[redacted]	[redacted]
CRT ≥ 400µm	[redacted]	[redacted]
Proportion of patients with at least 10 letter deterioration		
Full RESTORE population	3.5%	13.7%
CRT < 400µm	[redacted]	[redacted]
CRT ≥ 400µm	[redacted]	[redacted]

The Committee notes at paragraph 4.33 of the TAG that 'in order to draw reliable inferences about subgroups, it would need robust evidence demonstrating a plausible subgroup effect and ***accounting for differences in costs and utility in all aspects of the economic model****' (emphasis added).* Table 14 *summarises the approach to the subgroup analysis across these key parameters. The results of the cost effectiveness analysis by subgroup are presented in the tables below.*

Table 14: Key cost effectiveness parameters in subgroup analysis by retinal thickness

Parameter	Approach to subgroup analysis
Effectiveness (trial based)	Transition probability matrices are derived from year 1 of the RESTORE study, by subgroup.
Effectiveness/disease progression (beyond year 1)	Subsequent to year 1, the assumptions regarding treatment effect for subgroups are the same as the base case. Given clinical advice that vision tends to deteriorate despite laser in patients with thicker retina, it may be expected that effectiveness would not change over time and it may therefore be that this is a conservative assumption (biased against ranibizumab). New analysis of the RESTORE extension study could be undertaken to test this, however the proportion of patients receiving laser monotherapy in the extension is small given the study design (all patients could receive ranibizumab *prn*).
Utility values	Utility values in the model are associated to BCVA. The different distribution of BCVA at baseline between retinal thickness subgroups, and the basecase population, is reflected in this analysis.
Mortality	The evidence for mortality risk in patients with DMO is very limited. No evidence was identified to support an assumption that mortality would be sufficiently different in patient subgroups defined by ocular characteristics as to require adjustment of the basecase assumptions.
Treatment frequency	[redacted] Treatment frequencies in years 2 and 3 remain the same as the basecase.

Table 15: Basecase cost-effectiveness results for patients with thicker retina (CRT ≥400 µm), with revised PAS

	Laser	Ranibizumab
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)		[redacted]
QALYs	[redacted]	[redacted]
QALY difference		[redacted]
BSE ICER (£)		8,881
Bilateral ICER (£)		**13,322**
Maximum number of injections per patient <£30k per QALY		**25**

Table 16: Basecase cost-effectiveness results for patients with thinner retina (CRT <400 µm), with revised PAS

	Laser	Ranibizumab
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)		[redacted]
QALYs	[redacted]	[redacted]
QALY difference		[redacted]
BSE ICER (£)		28,861
Bilateral ICER (£)		**43,292**

Table 17: Basecase cost-effectiveness results for patients with CRT 300-400 µm, with revised PAS*

	Laser	Ranibizumab
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)		[redacted]
QALYs	[redacted]	[redacted]
QALY difference		[redacted]
BSE ICER (£)		25,665
Bilateral ICER (£)		**38,497**

*Treatment frequency as basecase

Table 18: Basecase cost-effectiveness results for patients with CRT <300 µm, with revised PAS*

	Laser	Ranibizumab
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)		[redacted]
QALYs	[redacted]	[redacted]
QALY difference		[redacted]
BSE ICER (£)		47,030
Bilateral ICER (£)		**70,545**

*Treatment frequency as basecase

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