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 macular oedema (MO) secondary to retinal vein occlusion (RVO).

Following a positive recommendation by NICE for ranibizumab for the treatment of RVO, 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 RVO, in an analysis that incorporates the Appraisal Committee's preferred assumptions. The PAS will therefore facilitate patient access to optimal treatment for RVO. Should the list price rise, the percentage discount will rise accordingly. Should the list price fall, the percentage discount will fall accordingly to maintain a net price of* [redacted].

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 RVO, the PAS will apply to all supplies and preparations of ranibizumab applicable to all current and future indications.

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?

Once the NHS Trust signs a commercial agreement with Novartis Pharmaceuticals UK Ltd as per the standard NHS pharmacy procurement procedure the Trust will have access to ranibizumab at the PAS price. 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, needs to 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 RVO, 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.

Not applicable.

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.

Not applicable.

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.

The population to whom the PAS applies has been presented in the main submission of evidence.

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.

The economic model has been updated to reflect the assumptions that the Appraisal Committee considered to be the most plausible. A revised base case analysis is presented in section 4.7. 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.

A simple discount of [redacted] is applied to the list price of ranibizumab in the model. The revised base case includes the changes as described in Table 1 to reflect the Appraisal Committee's concerns. The model time horizon has also been changed to

lifetime in order to be consistent with previous appraisals in RVO (dexamethasone implant cost effectiveness analysis - TA229). 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 Appraisal Committee in the manner described in the ACD. Thus, we acknowledge that there are limitations to the approaches used in the revised base case. For example, new long term data from the HORIZON follow up trial has not been taken into account in the revised base case and this has been shown to lower the ICER to £20,911 per QALY gained (shown as a sensitivity analysis in Table 10).

Table 1: Summary of the Appraisal Committee's concerns and revisions to the base case

Concern	Base case assumption
"The Committee concluded on the basis of the trial data that most people are treated for BRVO or CRVO in their 'worse-seeing eye' and the assumption in the model of all people being treated in their 'better-seeing eye' was inappropriate" (4.14).	The original BSE-only base case has been changed to a BSE/WSE mix based on the expected proportion of patients in clinical practice being treated in the BSE at baseline (10%) and at 12 month (20%). These base case assumptions for BSE/WSE proportions now also closely match those accepted in the appraisal of dexamethasone intravitreal implant.
"The Committee concluded that the manufacturer's base-case analysis had failed to account for age adjustments in the utility values" (4.15).	The 'Brazier utilities', as published by Csozky Murray and colleagues, are used in the revised base case to reflect treatment of the BSE. These utilities have been fitted to a 10 letter change in BCVA (rather than the ≥15 letter change as used by the ERG).The difference in utility between the best and worst BCVA health states in WSE are assumed to be 0.3 (as used in previous submissions – DMO TA237).
The Committee raised concerns that the use of pooled transition probabilities during months 7-24 in the model may not be an appropriate method to estimate effectiveness of the grid laser photocoagulation (laser) arm beyond 6 months (4.16).	The revised base case uses unpooled transition probabilities for 7-24 months for BRVO: 0.5 mg arm data only for ranibizumab arm, with the standard of care arm set equal to that of the ranibizumab arm.
"The Committee agreed that it was appropriate to include mortality risk	WSE mortality due to visual impairment (as implemented by the ERG) has been incorporated into the model.

associated with the condition and with visual impairment in the 'worse-seeing eye". (4.18)	

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 clinical effectiveness data is unchanged from that used in the original submission. Although additional efficacy data for year 2 is now available from the HORIZON follow up clinical trial, this has not been incorporated into the model but is shown as a sensitivity analysis in Tables 10-11.

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.[1]

- 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 (table 3).

The revised base case analysis, incorporating the Committee's preferred assumptions and the revised PAS, suggests that ranibizumab is a cost effective alternative to grid laser and dexamethasone implant in BRVO, and best supportive care and dexamethasone implant in CRVO with an ICER below the £30,000 per QALY threshold.

Table 2: BRVO base-case cost-effectiveness results vs. Laser

	Ranibizumab	**Ranibizumab (with PAS)**	**Laser**
Total costs (£)	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]	
QALYs	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]		
ICER (£)	**£35,068**	**£23,073**	

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

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 3: BRVO base-case cost-effectiveness results vs. Dexamethasone

	Ranibizumab	Ranibizumab (with PAS)	Dexamethasone
Total costs (£)	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]	
QALYs	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]		
ICER (£)	**£16,664**	**£2,370**	

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

Table 4: CRVO base-case cost-effectiveness results vs. Best Supportive Care

	Ranibizumab	Ranibizumab (with PAS)	Best supportive care
Total costs (£)	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]	
QALYs	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]		
ICER (£)	**£21,796**	**£13,851**	

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

Table 5: CRVO base-case cost-effectiveness results vs. Dexamethasone

	Ranibizumab	Ranibizumab (with PAS)	Dexamethasone
Total costs (£)	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]	
QALYs	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]		
ICER (£)	**£20,155**	**£6,995**	

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

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

- the results for the intervention without the patient access scheme

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

- 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 6: BRVO base-case incremental results (without PAS)

	Total costs (£)	Total LY	Total QALYs				
				Incremental costs (£)	Incremental QALYs	ICER (£) versus laser (QALYs)	ICER (£) incremental (QALYs)
Laser	[redacted]	**17.725**	[redacted]				
Dexamethasone implant	[redacted]	**17.731**	[redacted]	[redacted]	[redacted]	**£131,108**	
Ranibizumab	[redacted]	**17.746**	[redacted]	[redacted]	[redacted]	**£35,068**	**£16,664**

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

Table 7: BRVO base-case incremental results (with PAS)

	Total costs (£)	Total LY	Total QALYs				
				Incremental costs (£)	Incremental QALYs	ICER (£) versus laser (QALYs)	ICER (£) incremental (QALYs)
Laser	[redacted]	**17.725**	[redacted]				
Dexamethasone implant	[redacted]	**17.731**	[redacted]	[redacted]	[redacted]	**£131,108**	
Ranibizumab	[redacted]	**17.746**	[redacted]	[redacted]	[redacted]	**£23,073**	**£2,370**

Table 8: CRVO base-case incremental results (without PAS)

	Total costs (£)	Total LY	Total QALYs				
				Incremental costs (£)	Incremental QALYs	ICER (£) versus BSC (QALYs)	ICER (£) incremental (QALYs)
Best supportive care	[redacted]	**16.805**	[redacted]				
Dexamethasone implant	[redacted]	**16.823**	[redacted]	[redacted]	[redacted]	**£24,297**	
Ranibizumab	[redacted]	**16.843**	[redacted]	[redacted]	[redacted]	**£21,796**	**£20,155**

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

Table 9: CRVO base-case incremental results (with PAS)

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus BSC (QALYs)	ICER (£) incremental (QALYs)
Best supportive care	[redacted]	**16.805**	[redacted]				
Dexamethasone implant	[redacted]	**16.823**	[redacted]	[redacted]	[redacted]	**£24,297**	
Ranibizumab	[redacted]	**16.843**	[redacted]	[redacted]	[redacted]	**£13,851**	**£6,995**

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: BRVO one way sensitivity analysis for ranibizumab vs. laser

	Incremental costs (£) (without PAS)	Incremental costs (£) (with PAS)	Incremental QALYs	ICER (£) (without PAS)	ICER (£) (with PAS)
Base case	[redacted]	[redacted]	[redacted]	**£35,068**	**£23,073**
Frequency of ranibizumab treatment in year 1, 3 injections	[redacted]	[redacted]	[redacted]	**£19,828**	**£13,610**
Frequency of ranibizumab treatment in year 1, 12 injections	[redacted]	[redacted]	[redacted]	**£47,260**	**£30,643**
Frequency of ranibizumab treatment in year 2, 3 injections	[redacted]	[redacted]	[redacted]	**£36,800**	**£23,975**
Frequency of ranibizumab treatment in year 2, 6 injections	[redacted]	[redacted]	[redacted]	**£45,233**	**£29,385**
Continued ranibizumab treatment in year 3, 1 injection	[redacted]	[redacted]	[redacted]	**£38,364**	**£25,321**
Administration costs, ranibizumab £96	[redacted]	[redacted]	[redacted]	**£31,189**	**£19,194**
Administration costs ranibizumab £288	[redacted]	[redacted]	[redacted]	**£38,947**	**£26,952**

	Incremental costs (£) (without PAS)	Incremental costs (£) (with PAS)	Incremental QALYs	ICER (£) (without PAS)	ICER (£) (with PAS)
Follow up costs, ranibizumab £76	[redacted]	[redacted]	[redacted]	**£26,522**	**£14,527**
Follow up costs, ranibizumab £227	[redacted]	[redacted]	[redacted]	**£43,728**	**£31,733**
Frequency of ranibizumab visits in year 2, 4	[redacted]	[redacted]	[redacted]	**£35,348**	**£23,353**
Frequency of ranibizumab visits in year 2, 8	[redacted]	[redacted]	[redacted]	**£37,588**	**£25,593**
Frequency of ranibizumab visits in year 3+, 0	[redacted]	[redacted]	[redacted]	**£22,172**	**£10,177**
Frequency of ranibizumab visits in year 3+, 4	[redacted]	[redacted]	[redacted]	**£47,964**	**£35,968**
Discount rate costs and benefits, 0%	[redacted]	[redacted]	[redacted]	**£26,402**	**£17,063**
Discount rate costs and benefits, 6%	[redacted]	[redacted]	[redacted]	**£41,480**	**£27,504**
Discount rate costs 3.5% Discount rate benefits, 0%	[redacted]	[redacted]	[redacted]	**£26,590**	**£17,495**
Scenario Analyses					
% of patients stopping after 3 months due to insufficient response (10%)	[redacted]	[redacted]	[redacted]	**£32,657**	**£21,626**
0.2 overall utility gain for WSE	[redacted]	[redacted]	[redacted]	**£46,778**	**£30,778**
100% treated in WSE	[redacted]	[redacted]	[redacted]	**£44,354**	**£30,458**
Ranibizumab treatment frequency in year 2, adjusted for discontinuations [redacted]	[redacted]	[redacted]	[redacted]	**£33,325**	**£21,991**
HORIZON data for year 2 TPMs	[redacted]	[redacted]	[redacted]	**£32,161**	**£20,911**

With the revised PAS, the cost effectiveness of ranibizumab vs. laser is observed to remain below £30,000 per QALY in the majority of sensitivity and scenario analyses (Table 10). As expected, the results are sensitive to the frequency of injections and the follow up costs and visits. For example, in BRVO, increasing the number of injections in year 1 to 12 pushes the ICER over the £30,000 per QALY willingness to pay threshold. However, based on clinical expert opinion, it is unlikely that patients would require 12 injections in their first year of treatment.

Table 11: BRVO one way sensitivity analysis for ranibizumab vs Dexamethasone

	Incremental costs (£) (without PAS)	Incremental costs (£) (with PAS)	Incremental QALYs	ICER (£) (without PAS)	ICER (£) (with PAS)
Base case	[redacted]	[redacted]	[redacted]	**£16,664**	**£2,370**
Frequency of ranibizumab treatment in year 1: 6 injections	[redacted]	[redacted]	[redacted]	**£9,400**	**Dominant**
Frequency of ranibizumab treatment in year 1: 12 injections	[redacted]	[redacted]	[redacted]	**£31,192**	**£11,391**
Frequency of ranibizumab treatment in year 2: 0 injections	[redacted]	[redacted]	[redacted]	**£8,011**	**Dominant**
Frequency of ranibizumab treatment in year 2: 6 injections	[redacted]	[redacted]	[redacted]	**£28,777**	**£9,892**
Frequency of ranibizumab visits in year 2: 4	[redacted]	[redacted]	[redacted]	**£15,329**	**£1,035**
Frequency of ranibizumab visits in year 2: 12	[redacted]	[redacted]	[redacted]	**£20,668**	**£6,374**
Frequency of dexamethasone treatment in year 1: 1	[redacted]	[redacted]	[redacted]	**£21,367**	**£7,074**
Frequency of dexamethasone treatment in year 1: 4	[redacted]	[redacted]	[redacted]	**£7,257**	**Dominant**
Frequency of dexamethasone treatment in year 2: 0	[redacted]	[redacted]	[redacted]	**£26,962**	**£11,334**
Frequency of	[redacted]	[redacted]	[redacted]	**£6,365**	**Dominant**

	Incremental costs (£) (without PAS)	Incremental costs (£) (with PAS)	Incremental QALYs	ICER (£) (without PAS)	ICER (£) (with PAS)
dexamethasone treatment in year 2: 4					
Frequency of dexamethasone visits in year 2: 4	[redacted]	[redacted]	[redacted]	**£17,998**	**£3,704**
Frequency of dexamethasone visits in year 2: 10	[redacted]	[redacted]	[redacted]	**£13,995**	**Dominant**
Administration costs (ranibizumab)	[redacted]	[redacted]	[redacted]	**£18,534**	**£4,240**
Administration costs (dexamethasone)	[redacted]	[redacted]	[redacted]	**£21,635**	**£7,341**
Scenario Analyses					
% of patients stopping after 3 months due to insufficient response (10%)	[redacted]	[redacted]	[redacted]	**£13,791**	**£646**
0.2 overall utility gain for WSE	[redacted]	[redacted]	[redacted]	**£21,301**	**£3,029**
100% treated in WSE	[redacted]	[redacted]	[redacted]	**£22,080**	**£5,849**
Ranibizumab treatment frequency in year 2, adjusted for discontinuations [redacted]	[redacted]	[redacted]	[redacted]	**£14,587**	**£1,081**
HORIZON data for year 2 TPMs	[redacted]	[redacted]	[redacted]	**£15,096**	**£1,599**

For the comparison to dexamethasone implant, the 'direction' of the sensitivity analysis results is again as expected; when the number of ranibizumab injections required is reduced, the ICER is reduced, whereas if the number of dexamethasone injections required is reduced, the ICER is increased. In all sensitivity and scenario analyses the ICER of ranibizumab compared to dexamethasone treatment remains well below the £30,000 willingness to pay threshold under all assumptions and the majority are below the £10,000 per QALY willingness to pay threshold.

Table 12: CRVO one way sensitivity analysis for ranibizumab vs. best supportive care

	Incremental costs (£) (without PAS)	Incremental costs (£) (with PAS)	Incremental QALYs	ICER (£) (without PAS)	ICER (£) (with PAS)
Base case	[redacted]	[redacted]	[redacted]	**£21,796**	**£13,851**
Frequency of ranibizumab treatment in year 1, 3 injections	[redacted]	[redacted]	[redacted]	**£11,826**	**£7,660**
Frequency of ranibizumab treatment in year 1, 12 injections	[redacted]	[redacted]	[redacted]	**£26,781**	**£16,946**
Frequency of ranibizumab treatment in year 2, 0 injections	[redacted]	[redacted]	[redacted]	**£15,791**	**£10,122**
Frequency of ranibizumab treatment in year 2, 6 injections	[redacted]	[redacted]	[redacted]	**£25,273**	**£16,010**
Continued ranibizumab treatment in year 3, 1 injection	[redacted]	[redacted]	[redacted]	**£23,587**	**£15,072**
Administration costs, £96	[redacted]	[redacted]	[redacted]	**£19,227**	**£11,282**
Administration costs, £288	[redacted]	[redacted]	[redacted]	**£24,366**	**£16,420**
Follow up costs, ranibizumab £76	[redacted]	[redacted]	[redacted]	**£13,701**	**£5,756**
Follow up costs, ranibizumab £227	[redacted]	[redacted]	[redacted]	**£29,999**	**£22,054**
Frequency of ranibizumab visits in year 2, 6	[redacted]	[redacted]	[redacted]	**£21,735**	**£13,790**
Frequency of ranibizumab visits in year 2, 12	[redacted]	[redacted]	[redacted]	**£23,564**	**£15,618**
Frequency of ranibizumab visits in year 3+, 2	[redacted]	[redacted]	[redacted]	**£15,073**	**£7,127**
Frequency of ranibizumab visits in year 3+, 6	[redacted]	[redacted]	[redacted]	**£28,520**	**£20,575**
Discount rate costs and benefits, 0%	[redacted]	[redacted]	[redacted]	**£16,121**	**£9,950**
Discount rate costs	[redacted]	[redacted]	[redacted]	**£26,029**	**£16,746**

	Incremental costs (£) (without PAS)	Incremental costs (£) (with PAS)	Incremental QALYs	ICER (£) (without PAS)	ICER (£) (with PAS)
and benefits, 6%					
Discount rate costs 3.5% Discount rate benefits, 0%	[redacted]	[redacted]	[redacted]	**£16,453**	**£10,455**
Scenario Analyses					
% of patients stopping after 3 months due to insufficient response (6%)	[redacted]	[redacted]	[redacted]	**£20,821**	**£13,266**
0.2 overall utility gain for WSE	[redacted]	[redacted]	[redacted]	**£28,848**	**£18,332**
100% treated in WSE	[redacted]	[redacted]	[redacted]	**£28,998**	**£19,763**
Ranibizumab treatment frequency in year 2, adjusted for discontinuations [redacted]	[redacted]	[redacted]	[redacted]	**£20,532**	**£13,066**

With the revised PAS, the cost effectiveness of ranibizumab vs. best supportive care is observed to remain well below the £30,000 per QALY willingness to pay threshold in all sensitivity and scenarios analyses (Table 12). As expected, the results are sensitive to the frequency of injections and the follow up costs and visits.

Table 13: CRVO one way sensitivity analysis for ranibizumab vs. dexamethasone

	Incremental costs (£) (without PAS)	Incremental costs (£) (with PAS)	Incremental QALYs	ICER (£) (without PAS)	ICER (£) (with PAS)
Base case	[redacted]	[redacted]	[redacted]	**£20,155**	**£6,995**
Frequency of ranibizumab treatment in year 1: 6 injections	[redacted]	[redacted]	[redacted]	**£11,899**	**£1,869**
Frequency of ranibizumab treatment in year 1: 12 injections	[redacted]	[redacted]	[redacted]	**£28,412**	**£12,122**
Frequency of ranibizumab treatment in year 2: 0	[redacted]	[redacted]	[redacted]	**£10,208**	**£819**

	Incremental costs (£) (without PAS)	Incremental costs (£) (with PAS)	Incremental QALYs	ICER (£) (without PAS)	ICER (£) (with PAS)
Frequency of ranibizumab treatment in year 2: 6	[redacted]	[redacted]	[redacted]	**£25,914**	**£10,571**
Frequency of ranibizumab visits in year 2: 6	[redacted]	[redacted]	[redacted]	**£18,136**	**£4,977**
Frequency of ranibizumab visits in year 2: 12	[redacted]	[redacted]	[redacted]	**£21,165**	**£8,005**
Frequency of dexamethasone treatment in year 1: 1	[redacted]	[redacted]	[redacted]	**£23,719**	**£10,560**
Frequency of dexamethasone treatment in year 1: 4	[redacted]	[redacted]	[redacted]	**£13,027**	**Dominant**
Frequency of dexamethasone treatment in year 2: 0	[redacted]	[redacted]	[redacted]	**£26,935**	**£13,775**
Frequency of dexamethasone treatment in year 2: 4	[redacted]	[redacted]	[redacted]	**£13,376**	**£216**
Frequency of dexamethasone visits in year 2: 4	[redacted]	[redacted]	[redacted]	**£21,165**	**£8,005**
Frequency of dexamethasone visits in year 2: 10	[redacted]	[redacted]	[redacted]	**£18,137**	**£4,977**
Administration costs (ranibizumab)	[redacted]	[redacted]	[redacted]	**£21,571**	**£8,411**
Administration costs (dexamethasone)	[redacted]	[redacted]	[redacted]	**£24,732**	**£11,572**
Scenario Analyses					

	Incremental costs (£) (without PAS)	Incremental costs (£) (with PAS)	Incremental QALYs	ICER (£) (without PAS)	ICER (£) (with PAS)
% of patients stopping after 3 months due to insufficient response (6%)	[redacted]	[redacted]	[redacted]	**£18,540**	**£6,026**
0.2 overall utility gain for WSE	[redacted]	[redacted]	[redacted]	**£25,947**	**£9,005**
100% treated in WSE	[redacted]	[redacted]	[redacted]	**£26,161**	**£11,133**
Ranibizumab treatment frequency in year 2, adjusted for discontinuations [redacted]	[redacted]	[redacted]	[redacted]	**£18,061**	**£5,695**

For the comparison to dexamethasone implant, the 'direction' of the sensitivity analysis results is again as expected; when the number of ranibizumab injections required is reduced, the ICER is reduced, whereas if the number of dexamethasone injections required is reduced, the ICER is increased. In all sensitivity and scenario analyses the ICER of ranibizumab compared to dexamethasone treatment remains well below the £30,000 willingness to pay threshold under all assumptions and the majority are below the £10,000 per QALY willingness to pay threshold.

It is important to note that the model costs have not been updated from the NHS Reference Costs used in the original submission in 2011, for consistency across the appraisal. However, recent NHS Reference Costs to 2010/11 and updates to the cost of blindness suggest that the base case ICER could be a conservative estimate of cost effectiveness.

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

The probability that ranibizumab is cost-effective in BRVO when compared to laser is 44.2% at a willingness-to-pay (WTP) threshold of £20,000 and 58.6% at a WTP

threshold of £30,000. For ranibizumab the probability of being cost-effective compared to best supportive care in CRVO is 67.9% and 82.0% at WTP thresholds of £20,000 and £30,000 respectively.

Table 14: Probability of cost effectiveness (with PAS)

	WTP = £0	WTP= £ 20,000	WTP= £ 30,000
BRVO: ranibizumab vs laser	0.0%	44.2%	58.6%
CRVO: ranibizumab vs best supportive care	0.0%	67.9%	82.0%

Figure 1a BRVO cost effectiveness acceptability curve – ranibizumab versus laser (with PAS)

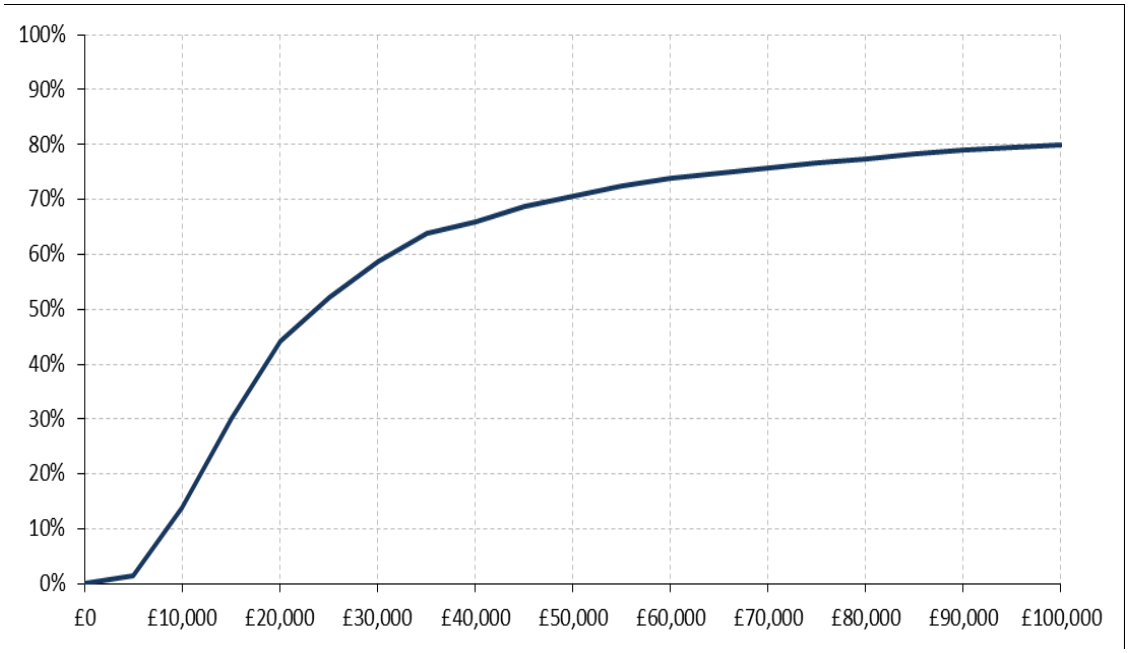


Figure 1b BRVO cost effectiveness scatter plot – ranibizumab versus laser (with PAS)

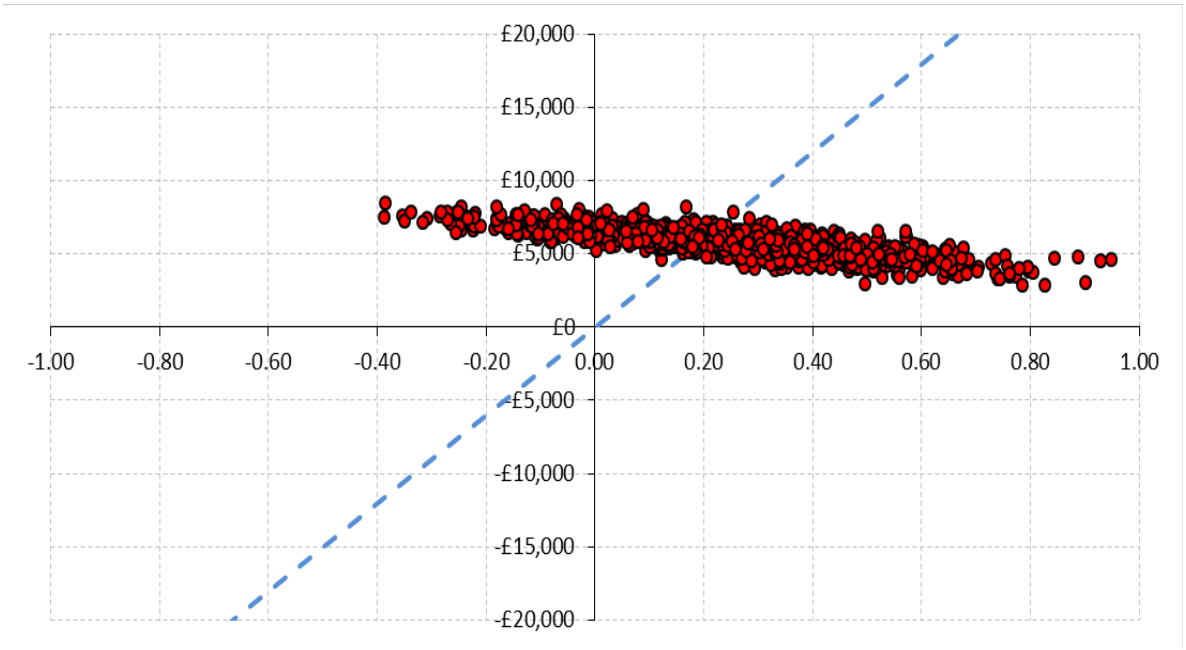


Figure 2a CRVO cost effectiveness acceptability curve – ranibizumab versus BSC (with PAS)

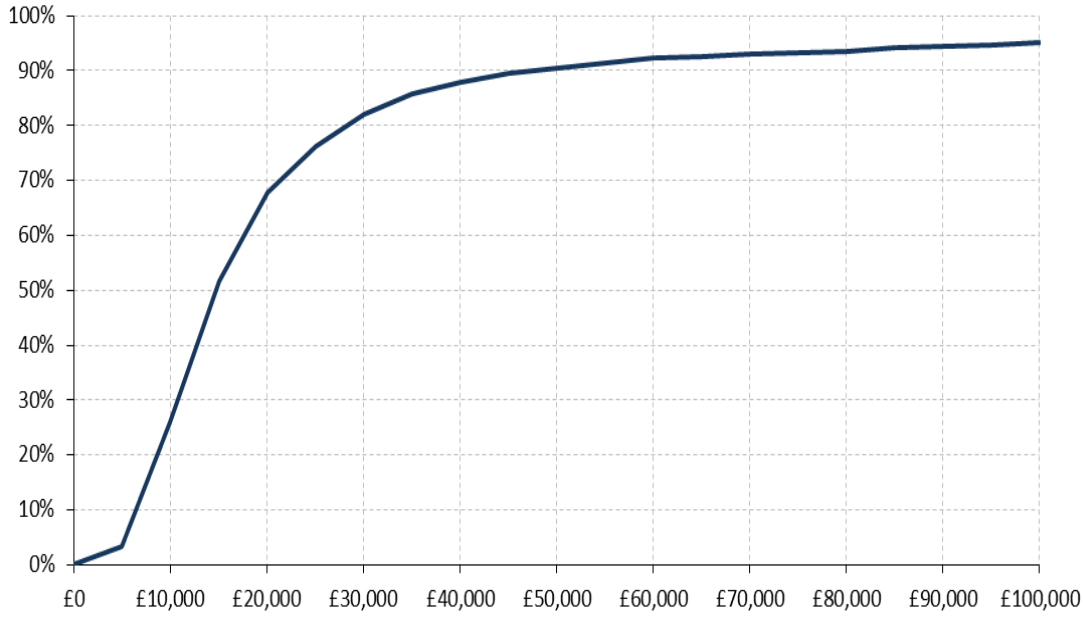
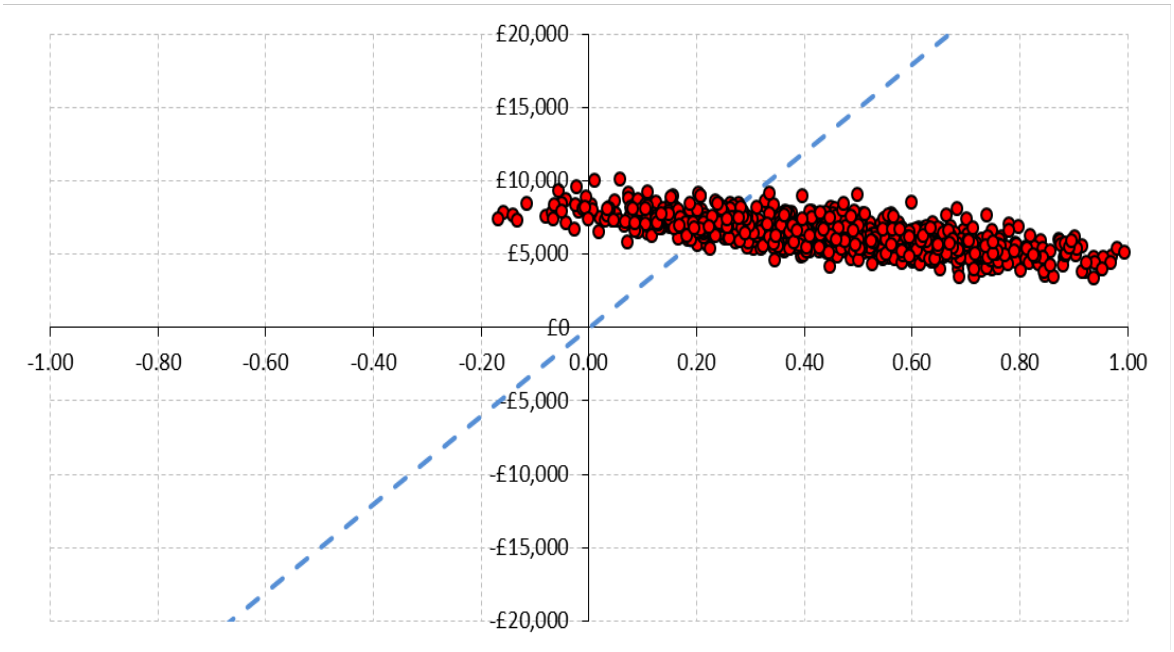


Figure 2b CRVO cost effectiveness scatter plot – ranibizumab versus BSC (with PAS)



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.

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (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.

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.

These are presented in sections 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 the most plausible (as described in section 4.3 above).

Appendices

4.14 Appendix A: Additional documents

4.14.1 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.

Not applicable.

4.15 Appendix B: Additional evidence

4.15.1 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 [1]. Thus, it is possible to derive Brazier utilities for each of the eight BCVA health states in the RVO 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 15. 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.

1 Czoski-Murray C, Carlton J, Brazier J, Young T, Papo NL, Kang HK. Valuing condition-specific health states using simulation contact lenses. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2009;12:793-9

Table 15: Utilities from Czoski-Murray et al calculated for the model health states (mean age of 65)

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**

Appendix B: Details of outcome-based schemes

4.15.2 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

4.15.3 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

4.15.4 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Not applicable.

For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable.

4.15.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Not applicable.

4.15.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Not applicable.

4.15.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable.

4.15.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)

- the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
- the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

4.15.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

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, section 4.8.