NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

- The population covered in the wording of the marketing authorisation for aflibercept is broader than the populations recruited to COPERNICUS and GALILEO. The population specified in the marketing authorisation are people with 'visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)'. The people recruited to the 2 phase III trials had not received prior treatment for macular oedema secondary to CRVO, that is, they were treatment naïve. There is an on-going study (NEWTON, a single-centre open label study) assessing aflibercept Injection for previously treated macular oedema associated with CRVO. This trial is due to be completed in December 2014 (the final data collection date for the primary outcome measure is December 2013) and was therefore not part of the manufacturer's submission.

Decision problem

- The manufacturer presented clinical and cost effectiveness evidence on aflibercept compared with ranibizumab and with dexamethasone, but excluded a comparison of aflibercept with bevacizumab and with clinical observation, even

though they were listed as comparators in the final scope issued by NICE. The manufacturer explained that it did not include bevacizumab or clinical observation as comparators because they are no longer considered routine or best practice since the publication of positive NICE guidance on the use of ranibizumab (TA 283) and dexamethasone (TA 229) in this condition. Is it appropriate for the manufacturer to exclude bevacizumab and clinical observation as comparators?

Clinical effectiveness

- The proportion of patients with severe ischemia in the COPERNICUS and GALILEO trials may be lower than the proportion of patients with severe ischemia and central retinal vein occlusion (CRVO) in England and Wales. Is it appropriate to generalise the results of the cost-effectiveness analysis, which is based on these trials, to include patients with severe ischemia?

Cost effectiveness

- In the manufacturer's model, any net gain in visual acuity at 6 months broadly persists through the model lifetime. Is it reasonable to assume there is a lifetime benefit of treatment from 1 year of treatment?
- The manufacturer's model incorporates the relative risk of gaining 15 or more letters at week 24, but it does not incorporate the relative risk of losing 15 letters or more at week 24. The relative risk of gaining 15 letters or more is in favour of aflibercept, but the relative risk of losing 15 letters or more is in favour of ranibizumab and detrimental to dexamethasone. It is appropriate not to include the relative risk of losing 15 letters or more in the model?
- The manufacturer did not incorporate a stopping rule in the model. The summary of product characteristics (SPC) for aflibercept states that continued treatment is not recommended if there is no improvement in visual and anatomic outcomes over the course of the first 3 injections. This is similar to the current SPC for ranibizumab for the treatment of macular oedema secondary to retinal vein occlusion. The manufacturer highlights that no additional stopping rules were recommended in NICE appraisal guidance 283 (Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion). Is it

appropriate for the manufacturer not to include a stopping rule in its model, considering the details of the SPC?

- The SPC for aflibercept does not specify the maximum number of doses or the longest length of time a person can receive aflibercept for. It states that monthly treatment should continue until visual and anatomic outcomes are stable for 3 monthly assessments and thereafter the need for continued treatment should be considered. It also states that treatment may be continued with increasing treatment intervals to maintain a stable visual and anatomic outcome. The manufacturer's base-case analysis assumes only 1 year of treatment. The scenario analyses that lengthen this to 2 and 5 years rely upon expert opinion about dosing. How long would people be expected to receive aflibercept in clinical practice? Which assumption of treatment duration (1, 2, or 5 years) is most appropriate?
- The ERG considers the implementation of the health related quality of life data in the model may be unduly conservative.
  - In the base-case analysis, it is assumed that the EQ-5D data are the health related quality of life data for the 'worse-seeing eye'. As a consequence, this is only applied when the study eye is being modelled as the 'worse-seeing eye'. Should the study eye be modelled as the 'better-seeing eye', no health related quality of life changes are anticipated. The ERG highlight that this applies to relatively few patients: around 3% at baseline and 10% at week 24.
  - In the scenario analysis, it is assumed that the utility values from Czoski-Murray et al (2009) are the health related quality of life data for the 'better-seeing eye'. As a consequence, this is only applied when the study eye is being modelled as the 'better-seeing eye'. Should the study eye be modelled as the 'worse-seeing eye', no health related quality of life changes are anticipated.

  Is the implementation of the health related quality of life data in the model appropriate?
- The utility values in the manufacturer's base-case analysis were obtained from the EQ-5D data from GALILEO and the utility values used in one of the manufacturer's scenario analyses were obtained from Czoski-Murray et al. The ERG highlighted that utility values from Brown (1999) were used in NICE technology appraisal guidance 229 (Dexamethasone intravitreal implant for the

treatment of macular oedema caused by retinal vein occlusion) and in NICE technology appraisal guidance 283 (Ranibizumab for treating macular oedema caused by retinal vein occlusion). The Appraisal Committee for NICE technology appraisal guidance 283 accepted that the range of utility values would lie somewhere between those estimated by Czoski-Murray et al. and those from the Brown study, although it concluded that the utility values estimated from Czoski-Murray et al. were acceptable The ERG stated that values from Czoski-Murray et al. and Brown tend to worsen the cost effectiveness estimates for aflibercept. Which utility values are the most appropriate to use in the cost effectiveness analysis?

- The manufacturer assumed that 52.38% of administration visits for anti-VEGF therapy (ranibizumab and aflibercept) would take place in an outpatient setting and the remaining in a day-case setting. This results in an average weighted administration cost of £257. The ERG considers that all administration visits would take place in an outpatient setting, resulting in an administration cost of £181. In NICE technology appraisal guidance no 283, the ranibizumab administration visit was costed as an office-based outpatient procedure. What is the administration cost of aflibercept in UK clinical practice?

1 Background: clinical need and practice

1.1 Central retinal vein occlusion (CRVO) is a common vascular disorder which is caused by thrombosis of the central retinal vein where it passes through the back of the optic nerve. The thrombosis increases retinal capillary pressure, which can cause blood and plasma to be discharged into the macular. The increase in retinal capillary pressure caused by thrombosis can also trigger production of vascular endothelial growth factor (VEGF), which increases the permeability of existing blood vessels and mediates the growth of new blood vessels that may leak or bleed into the macular. The accumulation of fluid at the macular is called macular oedema, and it can lead to severe visual impairment.

1.2 CRVO can be categorised as either ischemic or non-ischemic. More than 90% of patients with ischemic CRVO may have a visual acuity of 6/60 or

worse. This means they will only be able to see an object at 6 meters that a person without any visual problems can see at 60 meters. One of the signs of ischemic CRVO is non-perfusion of the capillaries in the disc areas of the retina. In contrast, perfusion in the disc areas is an indication that CRVO is non-ischemic. Non-ischemic CRVO may resolve completely without any complications or may progress to the ischemic type.

1.3 The incidence of macular oedema secondary to CRVO is estimated to be 12 per 100,000 people. This means that around 6,720 people in England Wales will develop the condition each year. The risk of CRVO typically increases with age, with over 90% of people with CRVO aged above 50 years. It occurs slightly more frequently in males than in females and shows no racial preference.

1.4 The impact of vision loss associated with CRVO can have a profound effect on vision-related quality of life. People may struggle with daily tasks, lose confidence and become increasingly dependent on family and carers.

1.5 Current treatment options aim to preserve vision and prevent complications. Dexamethasone intravitreal implant and ranibizumab are recommended as treatment options for macular oedema following central vein occlusion in NICE technology appraisal guidance 229 and 283 respectively. Other medical interventions may include intravitreal injections of bevacizumab, which is not licensed for the treatment of any ocular condition.

2 The technology

2.1 Aflibercept solution for injection (Eylea, Bayer) is a vascular endothelial growth factor (VEGF) inhibitor. It prevents the inappropriate growth of new blood vessels in the retina. Aflibercept has a UK marketing authorisation for ‘the treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)’. After the initial injection, treatment is given monthly. The summary of product characteristics states that the interval between two doses should not be shorter than one month.

If there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended. Monthly treatment continues until visual and anatomic outcomes are stable for three monthly assessments. Thereafter the need for continued treatment should be reconsidered.

2.2 Aflibercept is administered as a single 2 mg intravitreal injection. Each vial of aflibercept contains 4 mg in 0.1 ml, providing a usable amount to deliver a single dose of 0.05 ml containing 2 mg aflibercept. The summary of product characteristics states that monitoring is recommended at the injection visits and that the monitoring schedule should be determined by the treating physician based on the individual patient's responses.

2.3 Adverse reactions to treatment are mostly limited to the eye. The summary of product characteristics lists the following adverse reactions for aflibercept: conjunctival haemorrhage, eye pain, retinal pigment epithelium tear, vitreous haemorrhage, and retinal degeneration. Contraindications for aflibercept include hypersensitivity to the active substance or any of its excipients, active or suspected ocular or periocular infection, and active severe intraocular inflammation. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The list price of aflibercept 40 mg/ml is £816.00 per 0.1 mL vial (excluding VAT; 'British national formulary' [BNF] edition 65). The manufacturer of aflibercept solution for injection has agreed a patient access scheme with the Department of Health which makes aflibercept solution for injection available with a discount applied to the list price. The level of discount is commercial-in-confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of aflibercept within its licensed indication for the treatment of visual impairment due to macular oedema caused by central retinal vein occlusion.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults with visual impairment due to macular oedema caused by central retinal vein occlusion	
Intervention	Aflibercept solution for injection	
Comparators	Dexamethasone implant Ranibizumab Bevacizumab (for intravitreal injection) Clinical observation	Ranibizumab Dexamethasone implant

The manufacturer considered ranibizumab to be the main comparator. It stated that dexamethasone is not the main comparator because ranibizumab dominated dexamethasone in NICE technology appraisal guidance 283 (Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion) and because dexamethasone has potentially substantial side effects including increased intraocular pressure and cataract. The ERG agreed with the manufacturer that ranibizumab is the main comparator. The ERG highlighted that dexamethasone may be used in patients who do not respond to anti-VEGF drugs.

The manufacturer stated that bevacizumab should not be included as a comparator in the appraisal because it is no longer considered routine or best practice in the NHS. It also stated that bevacizumab is not licensed for use in ocular conditions and has not been appraised by NICE for use in eye conditions. In addition, the manufacturer stated that bevacizumab was not included in a comparison with ranibizumab in NICE technology appraisal guidance 283 as there was insufficient evidence to make robust comparisons, and that the 2 new studies of bevacizumab were too small and poorly designed to provide enough new evidence.

The manufacturer stated that observation should not be included as a comparator because there are 2 treatments recommended by NICE and so patients with CRVO are likely to be treated. The ERG noted that patients may be kept under observation if there were contraindications to anti-VEGF treatment (such as allergy and eye infections) or if they refused intravitreal treatment.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Outcomes	Visual acuity (the affected eye) Visual acuity (the whole person) Need for pan-retinal photocoagulation Adverse effects of treatment Health-related quality of life Mortality	
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	

3.2 In this appraisal, the manufacturer has positioned aflibercept solution for injection as an alternative treatment to dexamethasone and ranibizumab for people with visual impairment due to macular oedema secondary to central retinal vein occlusion.

4 Clinical-effectiveness evidence

4.1 The manufacturer performed a systematic review for randomised controlled trials investigating the efficacy and safety of aflibercept in the treatment of central retinal vein occlusion (CRVO). Two randomised

controlled trials (COPERNICUS and GALILEO) were identified that were relevant to the decision problem.

4.2 COPERNICUS compared aflibercept with sham injection in people with macular oedema secondary to CRVO that had been diagnosed less than 9 months prior to the start of the study and who had not received previous treatment. The trial was a randomised, double-blind, multicentre study conducted in 6 non-European countries. None of the study centres were located in the UK. From week 0 to week 24, patients in the intervention group (n=114) received aflibercept every 4 weeks and patients in the comparator group (n=73) received a sham injection every 4 weeks. From week 24 to week 52 patients in both groups received aflibercept if they met protocol-specified retreatment criteria, and received a sham injection if retreatment was not indicated. After the first year, patients continued in a one year extension phase (up to 100 weeks) with as needed dosing (no sham injection). Patients were retreated with aflibercept if any of the following conditions were met: increase of 50 micrometres or more in central retinal thickness on optical coherence tomography (OCT) compared with lower previous measurement, new or persistent cystic retinal damages of sub-retinal fluid on OCT or persistent diffuse oedema of 250 micrometres or more in the central subfield on OCT, or a loss of 5 letters or more or a gain of 5 letters or more between the current and most recent visit. All patients were eligible to receive pan retinal photocoagulation (PRP) at any time if they developed neovascularisation. The average age of the patients was 66.3 years and the majority of patients were male (57%). The mean best-corrected visual acuity (BCVA) at baseline was 50.0 letters and 68% of patients had perfused retinal occlusion, which was defined by the trial authors as less than 10 disc areas of capillary non-perfusion on fluorescein angiography. The manufacturer did not report any statistically significant differences in the baseline characteristics between the 2 groups.

4.3 GALILEO compared aflibercept with sham injection in patients with macular oedema secondary to CRVO that had been diagnosed less than

9 months prior to the start of the study and who had not received previous treatment. The trial was a randomised, double-blind, multicentre study conducted in 10 European and Asian-Pacific countries. None of the study centres were located in the UK. From week 0 to week 24, patients in the intervention group (n=103) received aflibercept every 4 weeks and patients in the comparator group (n=68) received a sham injection every 4 weeks. From week 24 to week 52, patients in the intervention group received aflibercept if they met protocol-specified retreatment criteria, or sham injection. Patients were assessed monthly using retreatment criteria as in COPERNICUS. Patients in the comparator group continued to receive sham injection from week 24 to week 52. From week 52 to 76, both groups received aflibercept every 8 weeks. All patients were eligible to receive PRP at any time if they developed neovascularisation. The average age of the patients was 61.5 years and the majority of patients were male (56%). The mean BCVA at baseline was 52.2 letters. Perfused retinal occlusion, defined by the trial authors as less than 10 disc areas of capillary non-perfusion on fluorescein angiography, was present in 86% of patients in the intervention group and 79% of patients in the comparator group. The manufacturer stated that there was a slight imbalance in mean central retinal thickness (CRT) between the 2 groups (683.20 micrometres in aflibercept compared with 638.66 micrometres in sham). The manufacturer stated that these values are considered to be close to the baseline CRT values from other CRVO trials, including COPERNICUS and CRUISE. The manufacturer did not report any statistically significant differences in the other baseline characteristics between the 2 groups.

4.4 The manufacturer used the same statistical analysis for the results from COPERNICUS and GALILEO and the intention to treat protocol was not used. In the primary efficacy analyses, data from all randomised patients who received any study medication and had a baseline assessment and at least 1 efficacy assessment after baseline were included (full analysis set, FAS). Participants were analysed according to the group to which they were randomised. In the sensitivity analyses, data from all patients in

the full analysis set who received at least 5 injections of study medication and did not have any major protocol violations or deviations were included (per protocol population, PP). Participants were analysed according to which treatment they received. In the analyses of safety data, data from all randomised patients who received any study medication were included (safety population, SAF). Participants were analysed according to which treatment they received.

4.5 The primary outcome of both COPERNICUS and GALILEO was the proportion of eyes with a gain of 15 letters or more in BCVA from baseline to week 24. Secondary outcomes in both trials included mean change from baseline in BCVA, central retinal thickness (CRT), the proportions of patients progressing to ocular neovascularisation, and vision related quality of life (National Eye Institute Visual Functioning Questionnaire [NEI VFQ-25], EQ-5D [in GALILEO only]) and safety parameters. Tertiary efficacy endpoints were all of the secondary outcomes at 52 weeks. Time to development of anterior segment neovascularisation or requirement of pan-retinal photocoagulation and selected subscales of the NEI VFQ-25 were also tertiary endpoints in GALILEO.

4.6 A summary of the results for the primary outcome (that is, the proportion of patients with a gain of 15 or more letters) is shown in table 1 for primary endpoint (week 24) and table 2 for other endpoints (weeks 52, 76 and 100). A summary of results for the secondary outcomes (mean change from baseline in BCVA, CRT and the proportions of patients progressing to ocular neovascularisation) is shown in table 3 and for other endpoints (weeks 52, 76 and 100) for patients progressing to ocular neovascularisation in table 4.

Table 1 Summary of results for primary outcome at 24 weeks from COPERNICUS and GALILEO (full analysis set)

Outcome	COPERNICUS		GALILEO	
	Aflibercept	**Sham**	**Aflibercept**	**Sham**
Patients gaining 15 or more letters (n, %)	64/114 (56%)*	9/73 (12%)	62/103 (60%)**	15/68 (22%)
*p<0.001 vs. sham (adjusted by N America vs. rest of world and baseline BCVA >20/200 vs. ≤20/200) **p<0.0001 vs. sham (adjusted by Europe vs. Asia/Pacific and baseline BCVA >20/200 vs. ≤20/200)				

Table 2 Summary of results for primary outcome at other endpoints from COPERNICUS and GALILEO (full analysis set, last observation carried forward for weeks 52 and 76)

Outcome	COPERNICUS		GALILEO	
Patients gaining 15 or more letters				
From baseline to 52 weeks	**Aflibercept if needed, or sham**		**Aflibercept**	**Sham**
	63/114 (55%)*	22/73 (30%)	62/103 (60%)**	22/68 (32%)
From baseline to 76 weeks	Not reported		**Aflibercept if needed, or sham**	
			59/103 (57%)**	20/68 (29%)
From baseline to 100 weeks	**Aflibercept if needed, or sham**		Not reported	
	56/114 (49%)***	17/73 (23%)		
*p<0.001 **p=0.0004 ***p=0.0003				

Table 3 Summary of results for secondary outcomes at 24 weeks from COPERNICUS and GALILEO (full analysis set, last observation carried forward)

Outcome	COPERNICUS		GALILEO	
	Aflibercept	**Sham**	**Aflibercept**	**Sham**
Mean change in BCVA from baseline (letters, mean+SD)	+17.3 (12.8)*	-4.0 (18.0)	+18.0 (12.2)**	+3.3 (14.1)
Mean change in central retinal thickness (CRT) from baseline (µm, mean+SD)	-457.2 (NR)*	-144.8 (NR)	-448.6 [redacted]**	-169.3 [redacted]
Patients progressing to neovascularisation in the retina (n, %)	0***	5 (7%)	3 (3%)	3 (4%)
NR Not reported, SD Standard deviation *p<0.001 vs. sham **p<0.0001 vs. sham ***p=0.006 vs. sham				

Table 4 Summary of results for neovascularisation at other endpoints from COPERNICUS and GALILEO

Outcome	COPERNICUS		GALILEO	
Incidence of neovascularisation				
From baseline to 52 weeks	**Aflibercept if needed, or sham**		**Aflibercept**	**Sham**
	0	0	3 (3%)	3 (4%)
From baseline to 76 weeks	Not reported		**Aflibercept if needed, or sham**	
			2 (2%)	0
From baseline to 100 weeks	**Aflibercept if needed, or sham**		Not reported	
	6/114 (5%)	3 (4%)		
P values not reported for any comparisons				

4.7 Subgroup analyses by sex, age, ethnicity, geographic location, baseline BCVA, baseline perfusion status, and time since CRVO diagnosis were performed in both COPERNICUS and GALILEO. In all subgroups, the proportion of patients gaining 15 or more letters was consistent with the results seen for the overall population. Four of the subgroups had too few

patients to draw meaningful conclusions regarding the proportion of patients gaining 15 letters or more (BCVA≤20/200 in both COPERNICUS and GALILEO, 'rest of the world' in COPERNICUS, and Asia/Pacific in GALILEO). The subgroup analyses for the secondary outcomes were [redacted].

4.8 Quality of life was measured by NEI VFQ-25 in COPERNICUS and by NEI VFQ-25 and EQ-5D in GALILEO. A summary of results for the NEI VFQ-25 at the primary (week 24) and other endpoints (weeks 52, 76 and 100) is shown in table 5. A summary of the unadjusted EQ-5D values from the European subset of the GALILEO population at the primary (week 24) and other endpoints (weeks 52 and 76) is shown in table 6.

Table 5 Summary of NEI VFQ-25 results for health related quality of life from COPERNICUS and GALILEO

Outcome	**COPERNICUS**		**GALILEO**	
Quality of life				
Mean change in NEI VFQ-25 total score (mean, SD)				
From baseline to 24 weeks	**Aflibercept**	**Sham**	**Aflibercept**	**Sham**
	7.2 (12.1)*	0.8 (9.8)	7.5 (NR)*	3.5 (NR)
From baseline to 52 weeks	**Aflibercept if needed, or sham**		**Aflibercept**	**Sham**
	7.5 (NR)**	5.1 (NR)	7.8 (NR)***	4.5 (NR)
From baseline to 76 weeks	Not reported		**Aflibercept if needed, or sham**	
			[redacted]	[redacted]
From baseline to 100 weeks	**Aflibercept if needed, or sham**		Not reported	
	[redacted]	[redacted]		

NR Not reported, SD Standard deviation
*p=0.001 vs. comparator
**p value not significant vs. comparator
***p=0.0049 vs. comparator

Table 6 Unadjusted EQ-5D values from the European subset of the GALILEO population

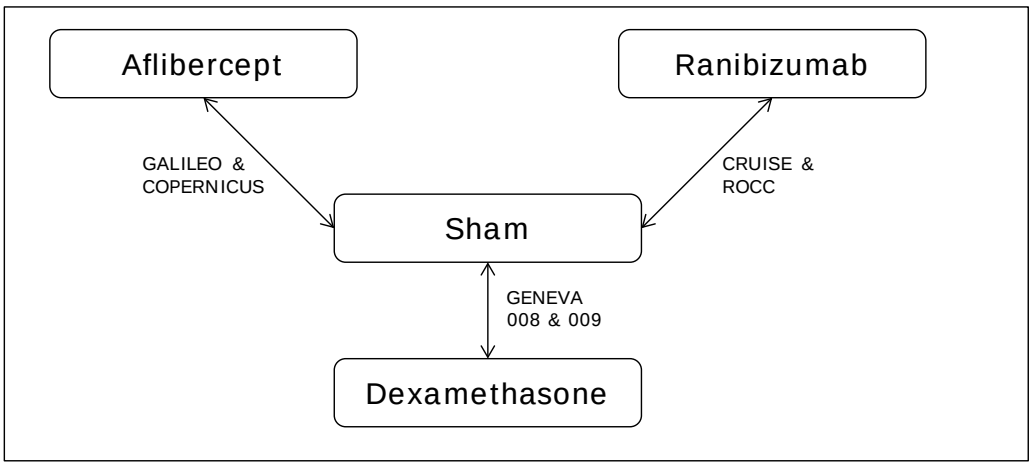
Time point	Mean EQ-5D value (SD)	
Baseline	**Aflibercept**	**Sham**
	[redacted]	[redacted]
Week 24	**Aflibercept**	**Sham**
	[redacted]	[redacted]
Week 52	**Aflibercept**	**Sham**
	[redacted]	[redacted]
Week 76	**Aflibercept if needed, or sham**	
	[redacted]	[redacted]
SD Standard deviation *p value not significant vs. sham		

4.9 The manufacturer performed a meta-analysis of the data from COPERNICUS and GALILEO at week 24 for the number of patients gaining 15 or more letters and the mean change in BCVA from baseline. The proportion of patients who gained 15 or more letters at 24 weeks was statistically significantly higher in the group receiving aflibercept compared with the group receiving sham injection (odds ratio 6.85; 95% confidence interval 4.08 to 11.51, relative risk 3.28; 95% confidence interval 2.25 to 4.79). There was a statistically significantly greater difference in BCVA from baseline to 24 weeks in patients receiving aflibercept compared with those receiving sham injection (weighted mean difference 17.52; 95% confidence interval 14.41 to 20.62).

4.10 The manufacturer performed a network meta-analysis to compare aflibercept with ranibizumab and dexamethasone, as head-to-head comparison data was not available from randomised controlled trials. Six high quality trials were included in the network meta-analysis. Two trials compared ranibizumab with sham injection (CRUISE and ROCC), 2 trials compared aflibercept with sham injection (COPERNICUS and GALILEO), and 2 trials compared dexamethasone intravitreal implant with sham injection (GENEVA 008 and GENEVA 009) (see figure 1). Data for bevacizumab were not included in the analysis as the manufacturer did not consider bevacizumab as the standard of care for CRVO and only 2

small studies of moderate to low quality were available (Epstein et al. [2012] and Wittstrom et al. [2012]).

Figure 1 Network of evidence in the manufacturer's network meta-analysis



4.11 The results of the network meta-analysis are shown in table 7. The analysis was only performed on 6-month (24 weeks) trial data because of the switching of participants between treatment groups in some of the trials. The manufacturer stated that the number of patients experiencing adverse events was too low to conduct a robust network meta-analysis on safety end points.

Table 7 Summary of results of the network meta-analysis

Comparison	Odds Ratio (95% CI)	Relative Risk (95% CI)	Mean change (95% CI)
Proportion of patients gaining 15 or more letters from baseline to 24 weeks			
Dexamethasone vs. aflibercept	[redacted]* [redacted] Fixed effects	[redacted]* [redacted] Fixed effects	NA
Ranibizumab vs. aflibercept	[redacted] [redacted] Fixed effects	[redacted] [redacted] Fixed effects	NA
Proportion of patients losing 15 or more letters from baseline to 24 weeks			
Ranibizumab vs. aflibercept	[redacted] [redacted] Random effects	[redacted] [redacted] Random effects	NA
Mean change in BCVA from baseline to 24 weeks			
Aflibercept vs. dexamethasone	NA	NA	[redacted]* [redacted] Random effects
Aflibercept vs. ranibizumab	NA	NA	[redacted] [redacted] Random effects
BCVA Best corrected visual acuity, CI Confidence interval, NA Not applicable * Result of statistical significance in favour of aflibercept			

4.12 A sensitivity analysis was performed on the network meta-analysis in which 1 of the trials comparing ranibizumab with sham injection (ROCC) was excluded from the analysis because of its small sample size. The statistical significance of the results of the sensitivity analysis did not differ from the base-case analysis.

4.13 The most common ocular treatment emergent adverse events in both trials and both groups were conjunctival haemorrhage, reduced visual acuity, eye pain, retinal haemorrhage, and increased intraocular pressure. The overall incidence of ocular treatment emergent adverse events [redacted] was [redacted] in the aflibercept and sham groups. [redacted] deaths occurred in the sham group of COPERNICUS – [redacted] from arrhythmia/acute myocardial infarction, [redacted] from oesophageal adenocarcinoma stage IV, and [redacted] from pneumonia. No deaths occurred in the aflibercept group of COPERNICUS or in either group in GALILEO. The manufacturer did not report whether the number of adverse events was statistically significantly different between the groups. A summary of the adverse events findings for COPERNICUS and GALILEO before patients were able to switch treatments, are shown in table 8.

Table 8 Summary of adverse events data from COPERNICUS and GALILEO

	COPERNICUS		GALILEO	
	Aflibercept (n=114)	**Sham (n=74)**	**Aflibercept (n=104)**	**Sham (n=68)**
Baseline to 24 weeks				
Any study drug-related treatment emergent adverse event (total)	[redacted]	[redacted]	[redacted]	[redacted]
Any study drug-related treatment emergent adverse event (study eye)	[redacted]	[redacted]	[redacted]	[redacted]
Any study drug-related treatment emergent adverse event (non-ocular)	[redacted]	[redacted]	[redacted]	[redacted]
Any injection-related treatment emergent adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Any study drug-related serious treatment emergent adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Any injection-related serious treatment emergent adverse event (study eye)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline to 52 weeks				
Any study drug-related treatment emergent adverse event (total)	NR	NR	[redacted]	[redacted]
Any study drug-related treatment emergent adverse event (study eye)	NR	NR	[redacted]	[redacted]
Any study drug-related treatment emergent adverse event (non-ocular)	NR	NR	[redacted]	[redacted]
Any injection-related treatment emergent adverse event	NR	NR	[redacted]	[redacted]
Any study drug-related serious treatment emergent adverse event	NR	NR	[redacted]	[redacted]
Any injection-related serious treatment emergent adverse event (study eye)	NR	NR	[redacted]	[redacted]
NR Not reported				

Evidence review group comments

4.14 The ERG noted that COPERNICUS and GALILEO are good quality trials.

4.15 The ERG noted that the mean time from diagnosis to treatment was quite short in COPERNICUS (aflibercept: 2.73 months; SD 3.09, sham injection: 1.88 months; SD 2.19) and GALILEO (aflibercept: 2.56 months; SD 2.95, sham injection: 2.88 months; SD 2.60), which might not reflect clinical practice in the UK.

4.16 The ERG was concerned that the proportion of patients with ischemia, in particular those with more serious ischemia, in COPERNICUS and GALILEO may be lower than is seen in routine practice. It is therefore not clear whether the results of COPERNICUS and GALILEO are applicable to CRVO patients with severe ischemia.

4.17 The ERG noted that there were no significant differences between the mean EQ-5D score in the aflibercept and sham injection groups. It highlighted that the EQ-5D score is known for being insensitive to changes in quality of life in eye conditions.

4.18 The ERG agreed with the manufacturer's assertion that the safety profile of aflibercept is similar to that of ranibizumab.

4.19 The ERG noted that the methods used by the manufacturer in the network meta-analysis were appropriate and the findings were presented correctly.

5 Comments from other consultees

5.1 The clinical specialists and professional groups stated that aflibercept offers an alternative treatment option, alongside ranibizumab and dexamethasone, for patients with macular oedema secondary to CRVO. They are aware that this would be particularly beneficial for patients whose disease did not respond to dexamethasone and/or ranibizumab. The clinical specialists and professional groups were in agreement that aflibercept has a decreased risk of intraocular pressure and cataracts compared with dexamethasone. They stated that aflibercept also has the potential to prevent neovascular complications such as iris and retinal neovascularisation. The clinical specialists and professional groups did not foresee any implementation issues in terms of facilities or equipment.

5.2 The patient groups stated that a diagnosis of CRVO causes a significant amount of stress and anxiety. They were in agreement that CRVO can lead to a loss of central vision and blindness, preventing people from working, driving, and taking part in other activities. They acknowledged

that there is also an increased risk of mental ill health, social isolation, and extra burden on health and social care from the increase risk of falls. The patient groups reported that all patients felt that the benefits of aflibercept outweighed the risks of having an intravitreal injection.

6 Cost-effectiveness evidence

6.1 The manufacturer identified 2 existing cost-utility studies of patients in the US with BRVO or diabetic macular oedema (Brown et al. [2002] and Smiddy et al. [2011]). The manufacturer judged that neither study suitably addressed the decision problem and so the studies were not used in the health economic analysis.

6.2 The manufacturer developed a cost utility Markov model that evaluated the cost effectiveness of aflibercept compared with ranibizumab in people with macular oedema secondary to CRVO. There were 25 health states in the model defined by the BCVA in both the eye receiving treatment (the study eye, SE) and the non-treated eye (the fellow eye, FE) in addition to the absorbing health state of death (see figure 2). The health states were defined by a 15 letter range in BCVA. The model had 4-weekly cycles and a time horizon of 30 years, which was effectively a lifetime horizon given the baseline age of the cohort being 64 years. Patients could move into an improved health state, remain in the same health state, or move into a worse health state (see figure 3). The BCVA for the patients' fellow eye was assumed to remain constant over time and so fellow eye involvement was not included in the model.

Figure 2 Health states used in the manufacturer's model (excluding death)

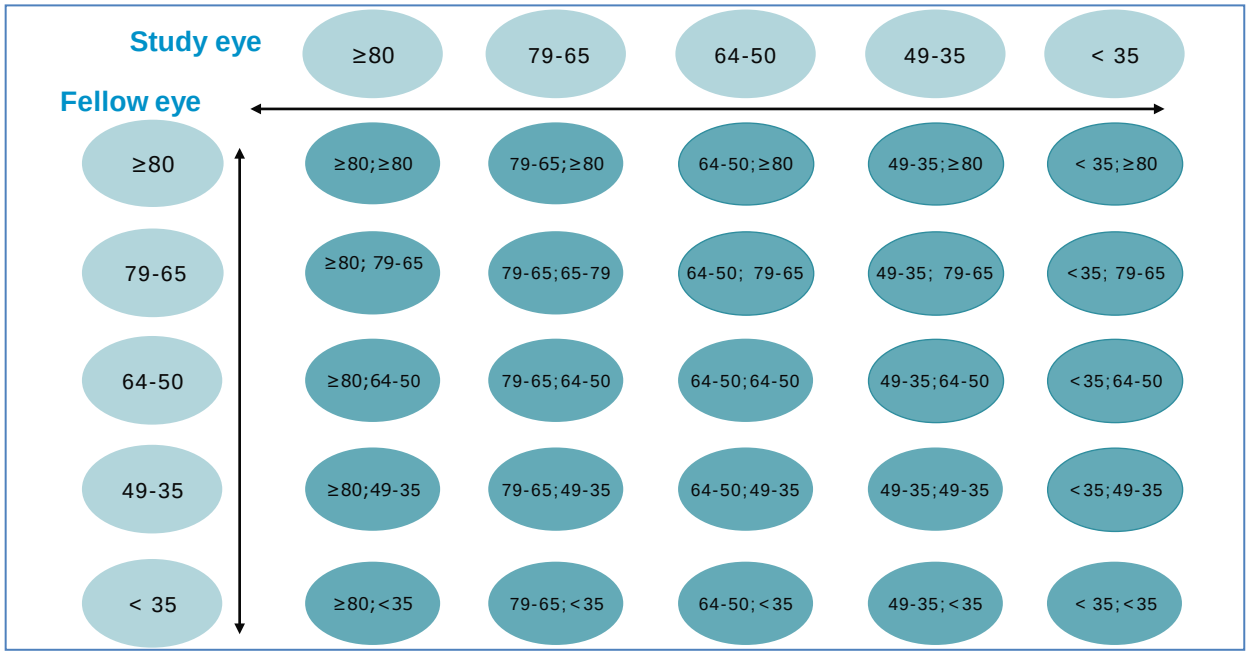
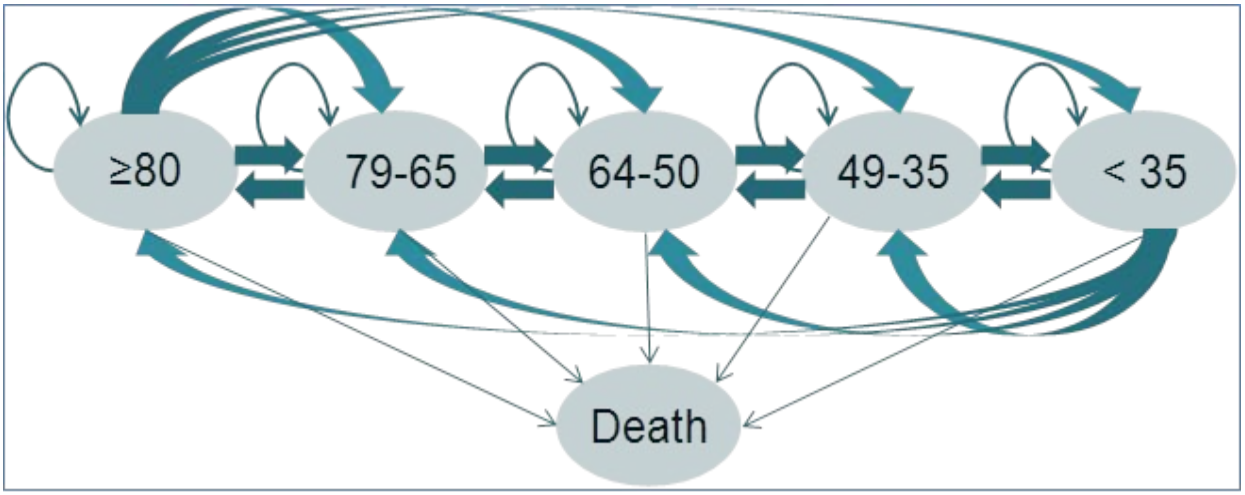


Figure 3 Movement between health states in the manufacturer's model



6.3 The baseline distribution of the patient population between the 25 health states of the model was inferred from the pooled COPERNICUS and GALILEO baseline distributions of the study eye and fellow eye. The model assumes that the distributions are independent, resulting in the inferred two-eyed patient distribution shown in table 9.

Table 9 Inferred baseline distributions used in the manufacturer's model

		Study Eye				
		HS1	**HS2**	**HS3**	**HS4**	**HS5**
Fellow eye	**HS1**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.4 Since the fellow eye was assumed to have a constant BCVA, only the BCVA of the study eye was modelled. The transition probabilities for aflibercept for the first 6 cycles (0 to 24 weeks) of the model were based on pooled data from COPERNICUS and GALILEO. To determine the transition probabilities for improvement in BCVA with ranibizumab for the first 6 cycles (0 to 24 weeks), the relative risk of gaining 15 or more letters with ranibizumab that was calculated in the network meta-analysis was applied to the aflibercept probabilities. The transition probabilities for moving to a worse BCVA with ranibizumab were assumed to be the same as with aflibercept. The transition probabilities for remaining in the same health state with ranibizumab were calculated by subtracting the transition probability for moving to a better health state and the transition probability for moving to a worse health state from 1. From cycle 6 to 13 (week 24 to 52) it was not possible to use pooled data from COPERNICUS and GALILEO because patients in COPERNICUS were able to change treatments after week 24. Participants in CRUISE were also able to change treatments after week 24. The manufacturer therefore chose to assume that, for both aflibercept and ranibizumab, patients' vision was maintained and participants remained in the same health state for cycles 6 to 13. From cycle 13 (week 52) onwards, it was assumed that for both aflibercept and ranibizumab, patients' BCVA deteriorated following a natural disease history progression that remained constant over time (Klein et al. [1991]).

6.5 The EQ-5D data collected in GALILEO was used for health related quality of life data in the economic model. The utility values used in the base-case analysis were based on the EQ-5D value averaged across all 4 time points (0, 24, 52, and 76 weeks) for the European population in both the aflibercept and sham injection groups of GALILEO. The utility values obtained from these scores were then analysed based on the 'worse-seeing eye' of the patients, to reflect that patients enrolled to the 2 aflibercept trials were predominantly tested in their 'worse-seeing eyes'. A total of 121 patients were included in the analyses, with 440 observations across all time points and across the 2 treatment groups. Each observation was assigned to 1 of the 5 health state BCVA ranges based on the BCVA achieved in the patient's 'worse-seeing eye'. The assignment was irrespective of whether the 'worse-seeing eye' was the study eye or fellow eye. For each BCVA range, the average utility values were then estimated across these observations. The 'worse-seeing eye' utility values from the EQ-5D trial data for each of the 5 health states are shown in table 10. The 'worse-seeing eye' utility values were attributed to the 25 health states in the model based on the lower of the two BCVA scores represented in a health state (see table 11). The manufacturer did not use the NEI VFQ-25 data collected in COPERNICUS and GALILEO as they stated that EQ-5D is the preferred measure in the NICE reference case. The manufacturer identified a relevant study by Czoski-Murray et al. (2009) which was used to obtain utility values used in the scenario analysis (see section 6.12).

Table 10 Manufacturer's base-case quality of life values: one-eyed health states

Health state	Quality of life
HS1	[redacted]
HS2	[redacted]
HS3	[redacted]
HS4	[redacted]
HS5	[redacted]

Table 11 Manufacturer's base-case quality of life values: two-eyed health states

		Study Eye				
		HS1	**HS2**	**HS3**	**HS4**	**HS5**
Fellow eye	**HS1**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.6 Discontinuation rates were not included in the model. The manufacturer stated that there was a low overall pooled discontinuation rate of 6.8% in COPERNICUS and GALILEO, and that in NICE technology appraisal guidance 283 (Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion), the Appraisal Committee had accepted modelling that did not explicitly account for the higher discontinuation rate for ranibizumab.

6.7 Adverse events were not modelled in the base-case analysis as the manufacturer states that anti-VEGFs (including ranibizumab and aflibercept) have similar safety profiles to each other. Intraocular pressure, cataract and retinal tear were modelled in the scenario analysis (see section 6.12).

6.8 Two costing studies were identified in a systematic review by the manufacturer, but neither was specific to the UK and therefore was not deemed to be useful (Fekrat et al. [2010] and Augustin et al. [2012]). Total costs for treatment were calculated from the unit costs for aflibercept or ranibizumab, administration, and a monitoring visit, multiplied by the number of treatment and monitoring visits required. The direct drug costs in the model were [redacted] (with the PAS) or £816 (without the PAS) for aflibercept and £742.17 for ranibizumab. The manufacturer assumed that 52.38% of administration visits for aflibercept and ranibizumab would take place in an outpatient setting and the remaining in a day-case setting. A

weighted average was used to derive an administration cost of £257 for either drug. Monitoring visit costs were £197.00 for either treatment.

6.9 The number of administration and monitoring visits required is shown in table 12. A one-stop model was applied, which assumed that administration costs can double as monitoring visits. A cost of [redacted] associated with blindness was applied each month for the first year when the 'better-seeing eye' was declared blind (BCVA of 35 letters or less). The cost of blindness for year 2 onwards was [redacted] each month.

Table 12 Frequency of administration and monitoring visits required

Intervention	Week 0 to 24	Week 24 to 52	Total for week 0 to 52
Administration			
Aflibercept	5.75*	2.55*	8.30
Ranibizumab	5.50**	3.30**	8.80
Monitoring			
Aflibercept	5.75*	3.50***	9.25
Ranibizumab	5.50**	4.40***	9.90

*Source: COPERNICUS and GALILEO
**Source: Campochiaro et al. 2011
***Source: physician survey

6.10 The manufacturer's base-case cost effectiveness results showed that aflibercept (price with the PAS) dominated ranibizumab (at list price) as it resulted in more QALYs ([redacted] compared with [redacted]) and lower costs ([redacted] compared with [redacted]). Without the PAS, aflibercept had more QALYs and higher costs ([redacted] compared with [redacted]) when compared with ranibizumab, resulting in an ICER of [redacted] per QALY gained. Results of the manufacturer's base-case results with and without the PAS are shown in table 13.

Table 13 Manufacturer's base-case deterministic results

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost per QALY (ICER)
With the aflibercept PAS					
Aflibercept	[redacted]	[redacted]	--	--	--
Ranibizumab	[redacted]	[redacted]	£2937	-0.054	Dominated
Without the aflibercept PAS					
Aflibercept	[redacted]	[redacted]	--	--	
Ranibizumab	[redacted]	[redacted]	[redacted]	-0.054	[redacted]

6.11 The manufacturer conducted one-way sensitivity analyses with and without the PAS price for aflibercept. When the PAS price was used, a net monetary benefit approach was used because aflibercept dominated ranibizumab in the base case. The sensitivity analyses showed that the key drivers of the model were the number of ranibizumab injections from 0 to 24 weeks and from 25 to 52 weeks, the relative risk of gaining 15 letters when comparing aflibercept with ranibizumab, the number of aflibercept injections from 25 to 52 weeks, and the number of monitoring treatments for ranibizumab from 0 to 52 weeks.

6.12 One sensitivity analysis reduced the price of ranibizumab from 0 to 50% in increments of 5%. When using the PAS price of aflibercept, the reduction in the price of ranibizumab did not affect the cost-effectiveness results for a reduction of up to 45%, and aflibercept remained dominant over ranibizumab. When the price of ranibizumab was reduced by 50%, aflibercept had higher costs and more QALYs than ranibizumab and had a with PAS ICER of £5871 per QALY gained. The results of sensitivity analyses for the other key drivers of the model were not reported by the manufacturer.

6.13 The manufacturer conducted three scenario analyses. The first scenario analysis used treatment durations of 2 years and 4 years rather than 1 year. The second scenario used utility values for the 'better-seeing eye' from Czoski-Murray et al. (2009), irrespective of whether the 'better-

seeing eye' was the study eye or the fellow eye (see table 14). The third scenario included adverse events (cataracts, intraocular pressure, and retinal tear) that were not included in the base-case analysis. The results of the scenario analyses for aflibercept with and without the PAS are shown in table 15.

Table 14 Czoski-Murray quality of life values

		Study Eye				
		HS1	**HS2**	**HS3**	**HS4**	**HS5**
Fellow eye	**HS1**	0.828	0.828	0.828	0.828	0.828
	HS2	0.828	0.735	0.735	0.735	0.735
	HS3	0.828	0.735	0.627	0.627	0.627
	HS4	0.828	0.735	0.627	0.519	0.519
	HS5	0.828	0.735	0.627	0.519	0.469

Table 15 Summary of results of the scenario analyses

Scenario	Incremental cost with aflibercept without PAS	Incremental cost with aflibercept with PAS	Incremental QALYs with aflibercept	Incremental cost per QALY (ICER) without PAS	Incremental cost per QALY (ICER) with PAS
2 year treatment duration	[redacted]	Not reported	0.054	[redacted]	Aflibercept dominates
4 year treatment duration	[redacted]	Not reported	0.054	[redacted]	Aflibercept dominates
Czoski-Murray utility values	[redacted]	Not reported	0.028	[redacted]	Aflibercept dominates
Adverse events	[redacted]	Not reported	0.054	[redacted]	Aflibercept dominates

6.14 The manufacturer presented a fourth scenario analysis in which aflibercept was compared with dexamethasone. In the deterministic analysis, aflibercept was associated with more QALYs (incremental QALYs: 0.189) and higher costs (incremental costs: [redacted] without PAS, not reported with PAS). This resulted in ICERs of £3236 per QALY gained (with PAS) and [redacted] per QALY gained (without PAS).

6.15 No subgroups were identified by the manufacturer for analysis.

Evidence review group comments and exploratory analyses

6.16 The ERG considered that the manufacturer's model was broadly reasonable. The ERG, however, identified the following areas of uncertainty in the manufacturer's model:

- Bevacizumab and clinical observation were not included as comparators. The ERG stated that bevacizumab has been widely used in the NHS and that clinical observation can be used in patients who have contraindications to anti-VEGFs and steroids, or if they refuse intravitreal treatment.
- Stopping rules were not used. The ERG state that stopping rules should be used for deterioration in visual acuity after 3 injections and if there is no fall in oedema fluid or CRT. The summary of product characteristics states that continued treatment is not recommended if there is no improvement in visual and anatomic outcomes over the course of the first 3 injections.
- Last observation carried forward method was used for the clinical effectiveness data but only observed data was used for the transition probability data. The ERG stated that the impact of using observed data in the model is unclear.
- Reapplying the relative risk of gaining 15 or more letters 6 times may have a compounding effect. The ERG stated that the impact of this compounding effect is unclear.
- Relative risk of losing 15 or more letters at 6 months is not included in the model. The ERG stated that whilst the relative risk of gaining 15 or more letters at 6 months favours aflibercept, the relative risk of losing 15 or more letters favours ranibizumab. This could affect the model results for the efficacy of aflibercept compared with ranibizumab.
- The assumption of lifetime duration of benefit may be unreasonable. The ERG stated that treatment was only received for 1 year and so it

may be optimistic to assume that the net gain at week 24 will remain for the lifetime of the patient.

- The assumption in the base-case analysis that changes in visual acuity of the study eye when it is the 'better-seeing eye' will have no impact on health related quality of life may not be accurate. The ERG stated that this assumption will tend to be conservative and reduce the estimated QALY gain from the more effective treatment.
- The assumption in the sensitivity analysis (where Czoski-Murray utility values were applied) that changes in visual acuity of the study when it is the 'worse-seeing eye' will have no impact on health related quality of life may not be accurate. The ERG stated that this will tend to be conservative and reduce the estimated QALY gain from the more effective treatment.
- Source of utility data. The ERG stated that, as a result of the cut off dates used in the manufacturer's literature searches, Brown (1999) was not identified as a source of utility data. It stated that Brown (1999) has been used in NICE technology appraisal guidance 283 and NICE technology appraisal guidance 229 and would have provided more conservative quality of life values.
- The number of dexamethasone administrations in year 1 appears to be overestimated. The ERG stated that the dexamethasone dosing as used in GENEVA may be more appropriate.
- The cost of aflibercept and ranibizumab administration appears to be an overestimate. The ERG stated that the outpatient administration costs could be reduced by costing them as 'Outpatient procedures: BZ23Z: Minor vitreous retinal procedures'.
- The cost of dedicated monitoring visits for aflibercept and ranibizumab appears to be an overestimate. The ERG stated that the dedicated monitoring visit costs could be reduced by costing them as 'RA23Z: Ultrasound Scan, less than 20 minutes'.
- The number of dedicated monitoring visits during months 7 to 12 for aflibercept and ranibizumab appears to be an overestimate

- The rate of cataract in the ranibizumab arm appears to be an overestimate. The ERG stated that Brown et al. (2010) report a lower rate of cataract, which is in line with NICE technology appraisal guidance 229.
- The duration of the quality of life impacts of raised intraocular pressure, cataracts and retinal tears appear to be underestimates. The ERG stated that Brown et al. (2007) assume that disutilities will apply for longer.
- The calculation used for the costs of raised intraocular pressure appears to be inappropriate. The ERG stated that the costs of medication were unnecessarily divided by 13 and the costs of inpatient therapies were divided by 6.
- The use of a blindness mortality multiplier appears to be inappropriate. The ERG stated that a weighted average mortality risk is calculated and applied to all patients regardless of their health state. This will raise the mortality rate to above what it should be for most patients and below what it should be for those with blindness. The ERG stated that this is likely to bias the analysis slightly towards the more effective treatment.
- The application of the costs of blindness in the aflibercept and ranibizumab arms appears to be inappropriate. The ERG stated that the manufacturer's model only considers the incidence events of blindness for aflibercept and ranibizumab, rather than considering the incident events and the prevalence of blindness as it does in the dexamethasone group.
- The costs of blindness appear to be underestimated. The ERG stated that McCrone et al. (2008) provides a better estimate of the costs of depression.

6.17 The ERG amended the manufacturer's model to overcome some of the uncertainties in the assumptions (see section 6.13) as shown in table 16.

Table 16 ERG's amendments to the manufacturer's model

Variable	Manufacturer's base case	ERG's revision
The number of dexamethasone administrations in year 1	4.00	1.86
Cost per aflibercept and ranibizumab administration	£257.45	£180.73
Cost per dedicated monitoring visit for aflibercept and ranibizumab	£197.00	£130.01
Number of dedicated monitoring visits for aflibercept (months 7 to 12)	2.43	0.95
Number of dedicated monitoring visits for ranibizumab (months 7 to 12)	2.03	1.10
Rates of cataract in the ranibizumab arm	3.3%	1.6%
Duration of quality of life impact of raised intraocular pressure	1 day per cycle (1day per month)	1 cycle (4 weeks)
Duration of quality of life impact of cataract	1 cycle (4 weeks)	3 cycles (12 weeks; 3 months)
Duration of quality of life impact of retinal tears	1 cycle (4 weeks)	4 cycles (16 weeks; 4 months)
Costs of raised intraocular pressure	£33	£4
Blindness mortality multipliers	1.54	0.00
Application of costs of blindness for aflibercept	To only incident cases of blindness	To both newly incident cases and prevalent cases
Application of costs of blindness for ranibizumab	To only incident cases of blindness	To both newly incident cases and prevalent cases
Costs of blindness in year 1	[redacted]	[redacted]
Costs of blindness from year 2 onwards	[redacted]	[redacted]

6.18 The ERG also corrected an error in the manufacturer's calculation of adverse event rates for aflibercept and dexamethasone from month 7 to 12. The ERG noted that the treatment rate for cataracts of 68% reported in the manufacturer's submission is not used in the manufacturer's model.

The ERG's base case shows that, without the PAS, aflibercept has a higher cost than ranibizumab but has a greater QALY gain, resulting in an

ICER of £[redacted] per QALY gained. With the PAS price of aflibercept and a 0 to 45% reduction in the list price of ranibizumab, aflibercept is less costly and has a greater QALY gain than ranibizumab, and therefore dominates ranibizumab. With the PAS price of aflibercept and a 50% reduction in the list price of ranibizumab, aflibercept is more costly and has a greater QALY gain, resulting in an ICER of £3820 per QALY gained (see table 17). The ERG's revisions to the model slightly improve the estimates of overall cost savings with aflibercept. The net QALY estimates are in line with those of the original model.

Table 17 ERG's base case for aflibercept compared with ranibizumab

Technology	Total cost	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost per QALY (ICER)
Without PAS price for aflibercept or ranibizumab					
Aflibercept	[redacted]	[redacted]	[redacted]	0.053	[redacted]
Ranibizumab	[redacted]	[redacted]	[redacted]	--	[redacted]
With PAS price for aflibercept and 0% reduction in price of ranibizumab					
Aflibercept	[redacted]	[redacted]	-£3049	0.053	Dominant
Ranibizumab	[redacted]	[redacted]	--	--	--
With PAS price for aflibercept and 10% reduction in price of ranibizumab					
Aflibercept	[redacted]	[redacted]	-£2398	0.053	Dominant
Ranibizumab	[redacted]	[redacted]	--	--	--
With PAS price for aflibercept and 15% reduction in price of ranibizumab					
Aflibercept	[redacted]	[redacted]	-£2073	0.053	Dominant
Ranibizumab	[redacted]	[redacted]	--	--	--
With PAS price for aflibercept and 20% reduction in price of ranibizumab					
Aflibercept	[redacted]	[redacted]	-£1748	0.053	Dominant
Ranibizumab	[redacted]	[redacted]	--	--	--
With PAS price for aflibercept and 25% reduction in price of ranibizumab					
Aflibercept	[redacted]	[redacted]	-£1432	0.053	Dominant
Ranibizumab	[redacted]	[redacted]	--	--	--
With PAS price for aflibercept and 30% reduction in price of ranibizumab					
Aflibercept	[redacted]	[redacted]	-£1098	0.053	Dominant
Ranibizumab	[redacted]	[redacted]	--	--	--
With PAS price for aflibercept and 35% reduction in price of ranibizumab					
Aflibercept	[redacted]	[redacted]	-£772	0.053	Dominant
Ranibizumab	[redacted]	[redacted]	--	--	--
With PAS price for aflibercept and 40% reduction in price of ranibizumab					
Aflibercept	[redacted]	[redacted]	-£447	0.053	Dominant
Ranibizumab	[redacted]	[redacted]	--	--	--
With PAS price for aflibercept and 45% reduction in price of ranibizumab					
Aflibercept	[redacted]	[redacted]	-£122	0.053	Dominant
Ranibizumab	[redacted]	[redacted]	--	--	--
With PAS price for aflibercept and 50% reduction in price of ranibizumab					
Aflibercept	[redacted]	[redacted]	£203	0.053	£3820
Ranibizumab	[redacted]	[redacted]	--	--	--
ICER Incremental cost effectiveness ratio; PAS Patient access scheme; QALYs Quality adjusted life years					

6.19 The ERG undertook sensitivity analyses around the relative risk of losing 15 or more letters at 6 months, lower and upper confidence intervals for the relative risk of gaining 15 or more letters at 6 months, the cost of administration, duration of treatment, number of injections required, number of monitoring visits, rate of worsening, adverse events, and the source of utility values. The ERG used the PAS price of aflibercept and reduced the list price of ranibizumab by a value of either 0% or 10 to 50% in increments of 5% (see table 18).

Table 18 ICERs from the ERG's sensitivity analyses for aflibercept compared with ranibizumab, for discounted prices of ranibizumab

Variable	ICER									
	0%	**10%**	**15%**	**20%**	**25%**	**30%**	**35%**	**40%**	**45%**	**50%**
Including the RR of losing 15 or more letters at 6 months	AD	AD	AD	AD	AD	AD	AD	AD	AD	£86,789
Using lower CI of RR for gain of 15 letters at 6 months	AD	AD	AD	AD	AD	AD	AD	AD	AD	£749
Using upper CI of RR for gain of 15 letters at 6 months	£62,932	£49,202	£42,337	£35,472	£28,607	£21,742	£14,877	£8012	£1147	RD
Using administration cost of £250	AD	AD	AD	AD	AD	AD	AD	AD	AD	£3176
Increasing duration of treatment to 2 years	AD	AD	AD	AD	AD	AD	AD	AD	AD	£3274
Increasing duration of treatment to 5 years	AD	AD	AD	AD	AD	AD	AD	AD	AD	AD
Using equal dosing for aflibercept and ranibizumab	AD	AD	AD	AD	AD	AD	AD	AD	£1364	£7128
Using equal dosing and monitoring for aflibercept and ranibizumab	AD	AD	AD	AD	AD	AD	AD	AD	£3562	£9326
Increasing post-treatment 4 weekly rate of visual worsening	AD	AD	AD	AD	AD	AD	AD	AD	AD	£3899
Including adverse events and increasing percentage of patients with raised IOP requiring treatment	AD	AD	AD	AD	AD	AD	AD	AD	AD	£3489
Using EQ-5D data from all patients	AD	AD	AD	AD	AD	AD	AD	AD	AD	£3144
Using Czoski-Murray utilities	AD	AD	AD	AD	AD	AD	AD	AD	AD	£5519

Using Czoski-Murray utilities with the WSE	AD	AD	AD	AD	AD	AD	AD	AD	AD	£3851
Using Brown utilities	AD	AD	AD	AD	AD	AD	AD	AD	AD	£8440
Using Brown utilities with the WSE	AD	AD	AD	AD	AD	AD	AD	AD	AD	£5076
AD Aflibercept dominates; CI Confidence interval; ICER Incremental cost effectiveness ratio; IOP Intraocular pressure; RD Ranibizumab dominates; RR Relative risk; WSE Worse-seeing eye										

6.20 The ERG also presented a deterministic ICER (see table 19) and sensitivity analyses (see table 20) for aflibercept compared with dexamethasone.

Table 19 ERG's deterministic ICER for aflibercept compared with dexamethasone

Technology	Total cost	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost per QALY (ICER)
Without PAS price for aflibercept					
Aflibercept	[redacted]	[redacted]	[redacted]	0.186	[redacted]
Dexamethasone	[redacted]	[redacted]	--	--	--
With PAS price for aflibercept					
Aflibercept	[redacted]	[redacted]	£2,285	0.186	£12,265
Dexamethasone	[redacted]	[redacted]	--	--	--
ICER Incremental cost effectiveness ratio; PAS Patient access scheme; QALYs Quality adjusted life years					

Table 20 ERG's sensitivity analyses for aflibercept (with PAS) compared with dexamethasone

Variable	ICER
Using lower CI of RR for gain of 15 letters at 6 months	£9,023
Using upper CI of RR for gain of 15 letters at 6 months	£24,991
Increasing duration of treatment to 2 years	£14,034
Increasing duration of treatment to 5 years	£18,699
Increasing post-treatment 4 weekly rate of visual worsening	£12,631
Including adverse events and increasing percentage of patients with raised IOP requiring treatment	£11,116
Using EQ-5D data from all patients	£9,760
Using Czoski-Murray utilities	£18,740
Using Czoski-Murray utilities with the WSE	£12,868
Using Brown utilities	£28,523
Using Brown utilities with the WSE	£16,833
Equal administration costs	£13,664
CI Confidence interval; ICER Incremental cost effectiveness ratio; RR Relative risk; WSE Worse-seeing eye	

7 Equality issues

7.1 No equality issues were identified at the scoping stage, or by the manufacturer, ERG, patient groups, clinical specialists or professional groups.

8 Innovation

8.1 The manufacturer states that aflibercept solution for injection is innovative as it has a different mode of action to other anti-VEGFs and it addresses a wider range of growth factors, including placental growth factor. The manufacturer states that the cost and capacity savings that could result from reduced monitoring with the use of aflibercept compared with other anti-VEGF treatments are unlikely to be captured by the QALY.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion. NICE technology appraisal guidance 283 (2013)
- Dexamethasone intravitreal implant for the treatment of macular oedema caused by retinal vein occlusion. NICE technology appraisal guidance 229 (2011)