NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

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

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Aflibercept solution for injection is recommended as an option for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion only if the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme.

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 solution for injection has a UK marketing authorisation for 'the treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)'.

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 of aflibercept. After the initial injection, treatment is given monthly. The summary of product characteristics states that the interval between 2 doses should not be shorter than 1 month. If there is no

improvement in visual and anatomic outcomes over the course of the first 3 injections, continued treatment is not recommended. Monthly treatment continues until visual and anatomical outcomes are stable for 3 monthly assessments. Thereafter the need for continued treatment should be reconsidered. The summary of product characteristics states that monitoring is recommended at the injection visits and that the monitoring schedule should be determined by the doctor responsible for the patient's care based on the response of the condition to treatment.

2.3 Adverse reactions to treatment are mostly limited to the eye. The summary of product characteristics lists the following adverse reactions as common or very common for aflibercept solution for injection for macular oedema secondary to CRVO: conjunctival haemorrhage, increased intraocular pressure, eye pain, vitreous detachment, vitreous floaters, increased lacrimation, and ocular hyperaemia. Contraindications for aflibercept solution for injection 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 solution for injection is £816.00 per 0.1-ml vial (excluding VAT; 'British national formulary' [BNF] edition 66). 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 The manufacturer's submission

The Appraisal Committee (section 8) considered evidence submitted by the manufacturer of aflibercept solution for injection (from here onwards referred to as aflibercept) and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

3.1 The manufacturer submitted evidence of clinical effectiveness for aflibercept compared with ranibizumab in people with macular oedema secondary to central retinal vein occlusion (CRVO). The main sources of evidence presented in the manufacturer's submission came from 2 randomised controlled trials that compared aflibercept with sham injection in people with macular oedema secondary to CRVO (COPERNICUS and GALILEO). In both trials the included patients had been diagnosed less than 9 months before the start of the trial and they had not received previous treatment for CRVO.

3.2 COPERNICUS was a randomised, double-blind, multicentre trial conducted in 6 non-European countries. 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 1-year extension phase (up to 100 weeks) with aflibercept as needed (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 or gain of 5 letters or more between the current and most recent visit. All patients were eligible to receive pan retinal photocoagulation at any time if they developed neovascularisation. The average age of the patients was 66.3 years and most 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 as fewer 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.

3.3 GALILEO was a randomised, double-blind, multicentre trial conducted in 10 European and Asian-Pacific countries. None of the study centres was 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 week 76, both groups received aflibercept every 8 weeks. All patients were eligible to receive pan retinal photocoagulation at any time if they developed neovascularisation. The average age of the patients was 61.5 years and most patients were male (56%). The mean BCVA at baseline was 52.2 letters. Perfused retinal occlusion, defined as fewer 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 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 central retinal thickness values from other CRVO trials, including COPERNICUS. The manufacturer did not report any statistically significant differences in the other baseline characteristics between the 2 groups.

3.4 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 trial medication and had a baseline assessment and at least 1 efficacy assessment after baseline were included (full analysis set). Data were analysed according to the group to which patients were randomised. In the sensitivity analyses, data from all patients in the full analysis set who received at least 5 injections of trial medication and did not have any major protocol violations or deviations were included (per protocol population). Data were analysed according to which treatment patients received. In the safety analyses, data from all randomised patients who received any trial medication were included (safety population). Data were analysed according to which treatment patients received.

3.5 The primary outcome of both COPERNICUS and GALILEO was the proportion of eyes with a gain of 15 or more letters in BCVA from baseline to week 24. Statistically significantly more patients gained 15 or more letters at 24 weeks with aflibercept than with sham in COPERNICUS (aflibercept 64/114 [56%] and sham 9/73

[12%], p<0.001 adjusted by region [North America compared with rest of the world] and baseline BCVA [greater than 20/200 compared with 20/200 or lower]). There were also statistically significantly more patients in GALILEO who gained 15 or more letters at 24 weeks with aflibercept than with sham (aflibercept 62/103 [60%] and sham 15/68 [22%], p<0.0001 adjusted by region [Europe compared with Asia/Pacific] and baseline BCVA [greater than 20/200 compared with 20/200 or lower]). 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 odds and relative risk of gaining 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]). Subgroup analysis showed that baseline perfusion status (presence or absence of ischaemia) did not appear to have any significant effect on response rates.

3.6 From week 24 to week 52, patients in both groups in COPERNICUS received aflibercept treatment as needed and patients in GALILEO continued to receive treatment according to their group allocation at the start of the trial. At 52 weeks, there were statistically significantly more patients who had gained 15 or more letters in the group initially allocated to receive aflibercept than in the group initially allocated to receive sham injection in COPERNICUS (aflibercept 63/114 [55%] and sham 22/73 [30%], p<0.001) and in GALILEO (aflibercept 62/103 [60%] and sham 22/68 [32%], p=0.0004).

3.7 From week 52 onwards, patients in both groups in COPERNICUS and GALILEO received aflibercept treatment as needed. At 76

weeks there were statistically significantly more patients who had gained 15 or more letters in the group initially allocated to receive aflibercept than in the group initially allocated to receive sham in GALILEO (aflibercept 59/103 [57%] and sham 20/68 [29%], p<0.0004). At 100 weeks there were statistically significantly more patients who had gained 15 or more letters in the group initially allocated to receive aflibercept than in the group initially allocated to receive sham in COPERNICUS (aflibercept 56/114 [49%] and sham 17/73 [23%], p=0.0003).

3.8 Secondary outcomes in both trials included mean change at 24 weeks from baseline in BCVA, central retinal thickness, and the proportions of patients progressing to ocular neovascularisation. The mean change in BCVA and the mean change in central retinal thickness from baseline to 24 weeks were statistically significantly greater in the aflibercept group compared with the sham group in both COPERNICUS and GALILEO. The percentage of patients progressing to neovascularisation at week 24 was statistically significantly greater in the sham group compared with the aflibercept group in COPERNICUS, but there was no statistically significant difference between the groups in GALILEO.

3.9 The manufacturer performed a network meta-analysis to compare aflibercept with ranibizumab and dexamethasone, because head-to-head comparison data were 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). Data for bevacizumab were not included in the analysis because the manufacturer did not consider

treatment with bevacizumab to be the standard of care for people with CRVO and only 2 small studies of moderate-to-low quality were available (Epstein et al. 2012 and Wittstrom et al. 2012). Epstein compared bevacizumab with sham in 60 patients and Wittstrom compared bevacizumab with pan-retinal photocoagulation in 19 patients.

3.10 The network meta-analysis was performed only on 6-month (24 weeks) trial data because of the switching of patients between treatment groups in some of the trials. For the comparison of ranibizumab with aflibercept, there was no statistically significant difference in the odds or relative risk of gaining 15 or more letters or of losing 15 or more letters. There was also no statistically significant difference in the mean change in BCVA from baseline to 24 weeks. For the comparison of dexamethasone with aflibercept, the odds and relative risk of gaining 15 or more letters from baseline to 24 weeks were statistically significantly smaller with dexamethasone and the mean change in BCVA was statistically significantly larger with aflibercept. The odds and relative risk of losing 15 or more letters were not reported. The results of the network meta-analysis were submitted as commercial in confidence and cannot be presented.

3.11 Impact on health-related quality of life was measured by NEI VFQ-25 in COPERNICUS and by NEI VFQ-25 and EQ-5D in GALILEO. From baseline to 24 weeks, there was a statistically significant greater mean change in NEI VFQ-25 score in the aflibercept group of both COPERNICUS (aflibercept 7.2, standard deviation [SD] 12.1, and sham 0.8, SD 9.8; p=0.001) and GALILEO (aflibercept 7.5, SD not reported, and sham 3.5, SD not reported; p=0.001). From baseline to 52 weeks, there was a statistically significant greater mean change in NEI VFQ-25 score in the aflibercept group

in GALILEO (aflibercept 7.8 and sham 4.5, p=0.0049) but there was no statistically significant difference in mean change in NEI VFQ-25 total score in COPERNICUS (aflibercept 7.5 and sham 5.1, p=0.216). The mean changes in NEI VFQ-25 total score at week 76 in GALILEO and week 100 in COPERNICUS were not statistically significantly different. EQ-5D values were reported for the European subset of the population in GALILEO and there were no significant differences in EQ-5D scores. The EQ-5D data were submitted as academic in confidence and therefore cannot be presented.

3.12 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. There were deaths from arrhythmia, acute myocardial infarction, oesophageal adenocarcinoma, and pneumonia in the sham group of COPERNICUS. The exact number of deaths in this group was submitted as academic in confidence and cannot be presented. 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.

3.13 The manufacturer stated that the number of patients who had adverse events in the trials included in the network meta-analysis was too low to conduct a robust network meta-analysis on safety end points.

Cost effectiveness

3.14 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) and the non-treated eye (the second eye), in addition to death. 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 that the baseline age of the cohort was 64 years. Patients could move into an improved health state, remain in the same health state, or move into a worse health state. The BCVA for the patients' second eye was assumed to remain constant over time and so second eye involvement was not included in the model.

3.15 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 second eye. The model assumes that the distributions are independent, resulting in an inferred 2-eyed patient distribution with the largest proportion of patients having BCVA of 64 to 50 in their study eye and BCVA of 80 or more in their second eye.

3.16 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 (see section 3.9) 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 week 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. Patients receiving ranibizumab 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 patients 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).

3.17 Because the second eye was assumed to have a constant BCVA, only the BCVA of the study eye was modelled. The manufacturer assumed an indefinite duration of treatment benefit, based on the treatment benefit seen at 24 weeks.

3.18 The EQ-5D data collected in GALILEO were 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 eye'. 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 the second 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 health states 1 to 5 were submitted as academic in confidence and cannot be presented. The 'worse-seeing eye' utility values were attributed to the 25 health states in the model based on the lower of the 2 BCVA scores represented in a health state. The manufacturer did not use the NEI VFQ-25 data collected in COPERNICUS and GALILEO because 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) that was used to obtain utility values used in the scenario analysis.

3.19 Adverse events were not modelled in the base-case analysis because the manufacturer stated that antivascular endothelial growth factors (anti-VEGFs; including ranibizumab and aflibercept) have similar safety profiles to each other. Raised intraocular pressure, cataracts and retinal tears were modelled in the scenario analysis.

3.20 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 needed. The direct drug costs in the model incorporated the confidential discount applied to the list price of aflibercept approved as part of the patient access scheme. 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 each drug. Monitoring visit costs were £197.00 for each treatment.

3.21 A one-stop model was applied, which assumed that administration visits can double as monitoring visits. It was assumed that aflibercept would need 5.75 administration and monitoring visits, and ranibizumab would need 5.50 administration and monitoring visits, from week 0 to week 24. From week 24 to week 52 it was assumed that aflibercept would need 2.55 administration visits and 3.50 monitoring visits, and that ranibizumab would need 3.30 administration visits and 4.40 monitoring visits. A cost associated with blindness was applied each month for the first and second year when the 'better-seeing eye' was declared blind (BCVA of 35 letters or fewer). The costs associated with blindness for year 1 and year 2 were submitted as commercial in confidence and cannot be presented.

3.22 The manufacturer's base-case cost-effectiveness results (incorporating the patient access scheme for aflibercept but not for ranibizumab) showed that aflibercept dominated (that is, was less expensive and more effective than) ranibizumab because it resulted in more quality-adjusted life years (incremental quality adjusted life years [QALYs] 0.054) and lower costs (incremental costs −£2937).

3.23 The manufacturer did not know the level of discount in the patient access scheme for ranibizumab because it is confidential so it applied a range of discounts to the list price of ranibizumab in its sensitivity analysis. When the manufacturer applied a discount to the list price of ranibizumab ranging from 0 to 50% in increments of 5%, aflibercept continued to dominate ranibizumab until the price of ranibizumab was discounted by 50%. When the price of ranibizumab was reduced by 50%, aflibercept had higher costs and more QALYs than ranibizumab, resulting in an incremental cost-effectiveness ratio (ICER) of £5871 per QALY gained. The ICERs

resulting from the sensitivity analyses for the other key drivers of the model were not reported by the manufacturer.

3.24 The manufacturer conducted one-way sensitivity analyses with and without the confidential discount applied to the list price of aflibercept. When using the discounted price of aflibercept, a net monetary benefit approach (calculated by multiplying the incremental QALYs by £20,000 and then subtracting the incremental costs) was used because aflibercept dominated ranibizumab in the base-case analysis. The results of the sensitivity analyses indicated that the model was sensitive to changes in the number of ranibizumab injections from 0 to 24 weeks and from 25 to 52 weeks, the relative risk of gaining 15 or more 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.

3.25 The manufacturer conducted 3 scenario analyses. The first scenario analysis used treatment durations of 2 years and 4 years rather than 1 year. This showed that aflibercept continued to dominate ranibizumab with incremental QALYs of 0.054 with 2 or 4 years of treatment (incremental costs with discounted aflibercept price were not reported). 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 second eye. In Czoski-Murray, a value of 0.828 is applied if either eye is in health state 1. If the highest BCVA in either eye was health state 2, a value of 0.735 was applied. If the highest BCVA in either eye was health state 3, a value of 0.627 was applied. If the highest BCVA in either eye was health state 4, a value of 0.519 was applied. If both eyes were in health state 5, a value of 0.469 was applied. Using Czoski-Murray utility values, aflibercept

continued to dominate ranibizumab with incremental QALYs of 0.028 (incremental costs with discounted aflibercept price not reported). The third scenario modelled the inclusion of the costs of adverse events (cataracts, intraocular pressure, and retinal tear) that were not included in the base-case analysis. Aflibercept continued to dominate ranibizumab with incremental QALYs of 0.054 (incremental costs with discounted aflibercept price not reported).

3.26 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 £612) which resulted in an ICER of £3236 per QALY gained.

3.27 No subgroups were identified by the manufacturer for analysis.

ERG critique of the manufacturer's submission

3.28 The ERG commented that the manufacturer did not include bevacizumab or clinical observation as comparators even though they were listed as comparators in the final scope issued by NICE. The ERG noted that the manufacturer stated 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 Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion (NICE technology appraisal guidance 283) and Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion (NICE technology appraisal guidance 229). The ERG noted that bevacizumab has been widely used in the NHS and that patients may be kept under observation if there are contraindications to anti-VEGF treatment

(such as allergy and eye infections) or if they refuse intravitreal treatment. The ERG questioned whether bevacizumab and clinical observation should have been included as comparators.

3.29 The ERG noted that it was not clear what proportion of patients in COPERNICUS and GALILEO had ischaemia or severe ischaemia, because different definitions of ischaemia and severe ischaemia exist. It suggested that the proportion of patients with ischaemia or severe ischaemia in the COPERNICUS and GALILEO trials may be lower than the proportion of patients with ischaemia or severe ischaemia and CRVO in England and Wales. The ERG questioned whether the results of COPERNICUS and GALILEO are applicable to patients with ischaemia or severe ischaemia.

3.30 The ERG highlighted that stopping rules were not used in the manufacturer's model. The manufacturer highlighted that no additional stopping rules were recommended in NICE guidance on ranibizumab (NICE technology appraisal guidance 283). The ERG noted from the summary of product characteristics that stopping rules should be used for deterioration in visual acuity after 3 injections and if there is no fall in oedema fluid or central retinal thickness. The ERG was aware that the summary of product characteristics also 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. The ERG questioned whether a stopping rule should have been implemented in the model.

3.31 The ERG considered that the manufacturer's model does not incorporate the relative risk of losing 15 or more letters. It highlighted that the relative risk of losing 15 or more letters is in favour of ranibizumab and detrimental to dexamethasone, and not including the relative risk of losing 15 or more letters could affect

the model results for the efficacy of aflibercept. The ERG questioned whether the relative risk of losing 15 or more letters should have been included in the model.

3.32 The ERG noted that, in the manufacturer's model, any net gain in visual acuity at 6 months broadly persists through the model lifetime. It highlighted that treatment was only received for 1 year. The ERG questioned whether it was reasonable to assume that the net gain at week 24 will remain for the lifetime of the patient.

3.33 The ERG suggested that the implementation of the health-related quality-of-life data in the manufacturer's model may be conservative. It highlighted that, 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'. The ERG noted that, as a consequence, this is only applied when the study eye is being modelled as the 'worse-seeing eye'. It also understood that it is assumed that the Czoski-Murray utility values are the health-related quality-of-life data for the 'better-seeing eye'. The ERG noted that, as a consequence, this is only applied when the study eye is being modelled as the 'better-seeing eye'. It questioned the appropriateness of this approach.

3.34 The ERG considered that 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. (2009). It noted that utility values from Brown (1999) were used in NICE guidance on dexamethasone (NICE technology appraisal guidance 229) and ranibizumab (NICE technology appraisal guidance 283). The ERG questioned which utility values are the most appropriate to use in the cost-effectiveness analysis.

3.35 The ERG argued that the costs of administration and monitoring for aflibercept and ranibizumab appeared to be overestimates. It stated that the outpatient administration costs could be reduced by costing them as 'Outpatient procedures: BZ23Z: Minor vitreous retinal procedures' and that the dedicated monitoring visit costs could be reduced by costing them as 'RA23Z: Ultrasound Scan, less than 20 minutes'.

3.36 The ERG noted that the calculation used for the costs of raised intraocular pressure appears to be inappropriate. It stated that the costs of medication were unnecessarily divided by 13 and the costs of inpatient therapies were divided by 6.

3.37 The ERG considered the application of the costs of blindness in the aflibercept and ranibizumab groups in the model appears to be inappropriate. It stated that the manufacturer's model only considers the incidence events of blindness for the aflibercept and ranibizumab groups, rather than considering the incident events and the prevalence of blindness as it does in the dexamethasone group.

3.38 The ERG argued that the costs of blindness appear to have been underestimated. It stated that the manufacturer used Meads and Hyde (2003) as their source of the costs of depression. The ERG stated that McCrone et al. (2008) provides a more recent and more accurate estimate of the costs of depression.

3.39 The ERG noted that 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 considered that all administration visits would take place in an outpatient setting,

resulting in an administration cost of £181. In NICE's guidance on ranibizumab, the ranibizumab administration visit was costed as an office-based outpatient procedure. The ERG queried which administration cost was the most appropriate.

3.40 The ERG conducted exploratory analyses, which involved the following modifications to the manufacturer's model:

- The number of dexamethasone administrations in year 1 was changed from 4.00 to 1.86.
- The cost per aflibercept or ranibizumab administration was changed from £257.45 to £180.73.
- The cost per dedicated monitoring visit for aflibercept or ranibizumab was changed from £197.00 to £130.01.
- The number of dedicated monitoring visits for aflibercept was changed from 2.43 to 0.95.
- The number of dedicated monitoring visits for ranibizumab was changed from 2.03 to 1.10.
- The cataract rate in the ranibizumab group was changed from 3.3% to 1.6%.
- The duration of quality of life impact of raised intraocular pressure was changed from 1 day per cycle to 1 cycle.
- The duration of quality of life impact of cataract was changed from 1 cycle to 3 cycles.
- The duration of quality of life impact of retinal tears was changed from 1 cycle to 4 cycles.
- The cost of raised intraocular pressure was changed from £33 to £4.
- The blindness mortality multipliers were changed from 1.54 to 0.00.

- The costs of blindness for aflibercept and ranibizumab were applied to both newly incident and prevalent cases of blindness instead of only the incident cases of blindness.
- The costs of blindness were increased. The costs were submitted as commercial in confidence and therefore cannot be presented.

The ERG also corrected an error in the manufacturer's calculation of adverse event rates for aflibercept and dexamethasone from month 7 to 12.

3.41 The ERG incorporated the confidential discount applied to the list price of aflibercept, but not the confidential discount for ranibizumab, in its exploratory analysis outlined in section 3.40. It showed that aflibercept dominated ranibizumab because it resulted in lower costs and higher QALYs (incremental costs −£3049, incremental QALYs 0.053).

3.42 The ERG was aware that the discounts agreed in the patient access schemes for aflibercept and ranibizumab are confidential. Therefore, it applied a discount ranging from 0 to 50% to the list price of ranibizumab in its exploratory analysis as well as applying the discount to the list price of aflibercept. With the discounted price of aflibercept and a 0 to 45% reduction in the list price of ranibizumab, aflibercept dominated ranibizumab because it is less costly (incremental costs ranged from −£3049 to −£122) and has a greater QALY gain (incremental QALYs 0.053) than ranibizumab. With the discounted price of aflibercept and a 50% reduction in the list price of ranibizumab, the ICER for aflibercept compared with ranibizumab was £3820 per QALY gained (incremental cost £203, incremental QALY 0.053).

3.43 The ERG carried out sensitivity analyses around the relative risk of losing 15 or more letters at 6 months, the administration cost,

duration of treatment, adverse events, and the source of utility values. The ERG used the discount to the list price of aflibercept and reduced the list price of ranibizumab by a value of either 0% or 10 to 50% in increments of 5%.

- When the relative risk of losing letters was included in the model and a discount of 0 to 45% was applied to the list price of ranibizumab, aflibercept dominated ranibizumab (incremental costs ranged from −£3005 to −£78, incremental QALYs 0.003). When a 50% discount was applied to the list price of ranibizumab, the ICER for aflibercept compared with ranibizumab was £86,789 per QALY gained (incremental cost £247, incremental QALY 0.003).
- When the administration cost was reduced in the model and a discount of 0 to 45% was applied to the list price of ranibizumab, aflibercept dominated ranibizumab (incremental costs ranged from −£3083 to −£156, incremental QALYs 0.053). When a 50% discount was applied to the list price of ranibizumab, the ICER for aflibercept compared with ranibizumab was £3176 per QALY gained (incremental cost £169, incremental QALY 0.053).
- When the duration of treatment was extended to 2 years and a discount of 0 to 45% was applied to the list price of ranibizumab, aflibercept dominated ranibizumab (incremental costs ranged from −£4422 to −£285, incremental QALYs 0.053). When a 50% discount was applied to the list price of ranibizumab, the ICER for aflibercept compared with ranibizumab was £3274 per QALY gained (incremental cost £175, incremental QALY 0.053).
- When the duration of treatment was extended to 5 years and a discount of 0 to 50% was applied to the list price of ranibizumab, aflibercept dominated ranibizumab (incremental costs ranged from −£6838 to −£31, incremental QALYs 0.053).

- When costs of adverse events were included in the model and a discount of 0 to 45% was applied to the list price of ranibizumab, aflibercept dominated ranibizumab (incremental costs ranged from −£3066 to −£139, incremental QALYs 0.053). When a 50% discount was applied to the list price of ranibizumab, the ICER for aflibercept compared with ranibizumab was £3489 per QALY gained (incremental cost £187, incremental QALY 0.053).
- When Czoski-Murray utility values with the 'worse-seeing eye' were used in the model and a discount of 0 to 45% was applied to the list price of ranibizumab, aflibercept dominated ranibizumab (incremental costs ranged from −£3049 to −£122, incremental QALYs 0.053). When a 50% discount was applied to the list price of ranibizumab the ICER for aflibercept compared with ranibizumab was £3851 per QALY gained (incremental cost £203, incremental QALY 0.053).
- When Brown utility values with the 'worse-seeing eye' were used in the model and a discount of 0 to 45% was applied to the list price of ranibizumab, aflibercept dominated ranibizumab (incremental costs ranged from −£3049 to −£122, incremental QALYs 0.040). When a 50% discount was applied to the list price of ranibizumab, the ICER for aflibercept compared with ranibizumab was £5076 per QALY gained (incremental cost £203, incremental QALY 0.040).

3.44 The ERG also presented a deterministic ICER for aflibercept compared with dexamethasone. Incorporating the patient access scheme for aflibercept, the ICER for aflibercept compared with dexamethasone was £12,265 per QALY gained (incremental cost £2285, incremental QALY 0.186).

3.45 The ERG also carried out exploratory analyses on the comparison of aflibercept with dexamethasone, incorporating the patient access

scheme for aflibercept. Increasing the duration of treatment to 2 years resulted in an ICER for the comparison of aflibercept with dexamethasone of £14,034 per QALY gained and increasing it to 5 years resulted in an ICER of £18,699 per QALY gained. For the comparison of aflibercept with dexamethasone, using Czoski-Murray utility values with the 'worse-seeing eye' resulted in an ICER of £12,868 per QALY gained, and with the 'better-seeing eye' resulted in an ICER of £18,740 per QALY gained. Using Brown utility values with the 'worse-seeing eye' resulted in an ICER of £16,833 per QALY gained, and with the 'better-seeing eye' resulted in an ICER of £28,523 per QALY gained.

3.46 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of aflibercept, having considered evidence on the nature of macular oedema secondary to central retinal vein occlusion (CRVO) and the value placed on the benefits of aflibercept by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee heard from patient experts about the problems associated with visual impairment caused by macular oedema. It heard that the loss of vision has a significant effect on the independence of people with the condition. The patient experts also stated that the condition affects the ability to drive, and take part in hobbies such as reading and going to the cinema. The patient experts commented that the condition can affect people of working age, as they may be unable to work and support their family, and

they may be unable to take time off work to attend regular follow-up or monitoring appointments. The patient experts acknowledged that although people may be worried about having an injection the eye, they are willing to receive injections to keep their sight. The Committee agreed that loss of vision caused by macular oedema secondary to CRVO seriously impairs health-related quality of life.

4.3 The Committee heard from clinical specialists that the current standard treatment for visual impairment caused by macular oedema secondary to CRVO is dexamethasone or antivascular endothelial growth factor (anti-VEGF) drugs, especially ranibizumab. The clinical specialists noted that the use of bevacizumab outside its marketing authorisation has decreased since NICE's guidance on Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion (NICE technology appraisal guidance 283) and Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion (NICE technology appraisal guidance 229) recommended ranibizumab and dexamethasone as options for treating people with CRVO. The clinical specialists stated that they are more likely to use ranibizumab than dexamethasone even though it has a higher frequency of injections, because they believe that it has a decreased risk of side effects such as raised intraocular pressure and cataracts. The Committee concluded the current standard treatment for visual impairment caused by macular oedema secondary to CRVO is ranibizumab, although dexamethasone is also used.

4.4 The Committee considered the comparators for the appraisal. It noted that the final scope issued by NICE included dexamethasone, ranibizumab, bevacizumab and clinical

observation as comparators, but that the manufacturer only included dexamethasone and ranibizumab as comparators in its economic analysis. The Committee noted that the manufacturer did not include clinical observation as a comparator because it was of the opinion that patients would receive treatment with either ranibizumab or dexamethasone because NICE had recommended them as treatment options. The Committee was aware that the manufacturer did not include bevacizumab in its submission. The Committee acknowledged that the manufacturer's rationale for not including bevacizumab as a comparator was that its use in the NHS was not routine or best practice. The Committee heard from the clinical experts that the use of bevacizumab has decreased since the publication of NICE's guidance on ranibizumab (NICE technology appraisal guidance 283) and dexamethasone (NICE technology appraisal guidance 229). Most importantly, the Committee was concerned that there were only 2 small trials for bevacizumab compared with sham injections, and no direct comparisons of aflibercept with intravitreal bevacizumab are currently available. The Committee concluded that there is currently insufficient evidence for bevacizumab to make the robust comparisons with aflibercept needed for a cost-effectiveness analysis.The Committee further concluded that ranibizumab and dexamethasone were appropriate comparators in this appraisal.

Clinical effectiveness

4.5 The Committee considered the populations in COPERNICUS and GALILEO. The Committee acknowledged that the trials did not exclude people with ischaemia or severe ischaemia. The Committee heard from the manufacturer that aflibercept was effective across the full trial populations of COPERNICUS and GALILEO. However, the Committee heard from the clinical

specialists and the Evidence Review Group (ERG) that the proportions of patients with ischaemia or severe ischaemia in the trials were uncertain because different definitions of ischaemia and severe ischaemia exist. The Committee accepted that aflibercept could be considered effective for all of the population included in the trials.

4.6 The Committee considered the evidence presented by the manufacturer on the clinical effectiveness of aflibercept. It acknowledged that the main sources of evidence came from the COPERNICUS and GALILEO randomised controlled trials, which compared aflibercept with sham injection in people with CRVO. The Committee noted that in both COPERNICUS and GALILEO, aflibercept was associated with statistically significantly more eyes gaining 15 or more letters at 24 weeks compared with sham injection. The Committee was aware that people in the sham groups could receive aflibercept after 24 weeks in COPERNICUS and after 52 weeks in GALILEO. The Committee agreed that aflibercept resulted in greater visual gains when it was given to patients soon after diagnosis. The Committee concluded that aflibercept is a clinically effective treatment for visual impairment caused by macular oedema secondary to CRVO compared with sham injection.

4.7 The Committee considered the evidence for the clinical effectiveness of aflibercept compared with ranibizumab and dexamethasone. It noted that evidence from direct comparisons was not available, and that a network meta-analysis was presented by the manufacturer. The Committee heard from the ERG that the methods used in the network meta-analysis were appropriate and that the analysis was well conducted. The Committee agreed that in the absence of a direct comparison, the results could be used to

inform decisions about the clinical effectiveness of aflibercept compared with ranibizumab and dexamethasone. The Committee agreed that given the nature of the evidence, there was some uncertainty about the clinical effectiveness of aflibercept compared with ranibizumab and dexamethasone, but concluded that there was no evidence that aflibercept was not as clinically effective as ranibizumab or dexamethasone.

4.8 The Committee considered the evidence for adverse effects associated with aflibercept. It noted that the overall frequency of adverse events in the COPERNICUS and GALILEO trials was low. The Committee heard from the clinical specialists that the safety profile of aflibercept is similar to that of ranibizumab, which is already licensed for use in this condition (see NICE guidance on ranibizumab [NICE technology appraisal guidance 283]). The Committee concluded that treatment with aflibercept had a similar adverse event profile to ranibizumab.

Cost effectiveness

4.9 The Committee considered the manufacturer's economic model and the critique and exploratory analyses performed by the ERG. The Committee noted that the manufacturer had presented a comparison of aflibercept with ranibizumab for its base-case analysis and a comparison of aflibercept with dexamethasone as a scenario analysis. The Committee acknowledged that the ERG had concerns about some of the assumptions made by the manufacturer in the base-case analysis. In particular, the ERG queried why:

- any net gain in visual acuity at 24 weeks was assumed to persist through the lifetime of the model

- the relative risk of losing 15 or more letters at 24 weeks was not included in the model
- the duration of treatment was assumed to be 1 year
- EQ-5D data from GALILEO was used as a source of utility values
- the costs of adverse events were not included in the model
- a stopping rule was not included in the model
- the estimated administration costs of aflibercept and ranibizumab were high
- the estimated costs of blindness were low.

The Committee considered each of these issues in turn, as detailed below.

4.10 The Committee discussed the manufacturer's assumption that the benefits of treatment at 24 weeks would continue indefinitely throughout the lifetime of the model. The Committee heard from the ERG that the assumption may be optimistic and that it would exaggerate the quality-adjusted life year (QALY) gain of aflibercept over ranibizumab and dexamethasone. The Committee acknowledged that a sensitivity analysis around the duration of benefit of treatment was not undertaken by the manufacturer or the ERG. The Committee heard from the ERG that if the benefits of treatment at 24 weeks had not been assumed to continue indefinitely it was unlikely to change the overall results of the manufacturer's base-case analysis because aflibercept would still dominate (be less expensive and more effective than) ranibizumab. The Committee accepted that it was not appropriate to assume that the duration of treatment benefit at 24 weeks would continue indefinitely but concluded that it was likely to have little impact on the cost-effectiveness estimates.

4.11 The Committee discussed how the manufacturer's model did not incorporate the relative risk of losing 15 or more letters. The Committee heard from the ERG that incorporating the relative risk of losing 15 or more letters into the model would ensure that the transition probabilities were correctly calculated. The ERG highlighted that including the relative risk of losing 15 or more letters in its exploratory analysis, which included the confidential discount applied to the list price for aflibercept, did not affect the dominance of aflibercept over ranibizumab except when a 50% reduction was applied to the list price of ranibizumab (see section 3.43). The Committee accepted that the relative risk of losing 15 or more letters should have been included in the manufacturer's model but concluded that including it was unlikely to change the dominance of aflibercept over ranibizumab.

4.12 The Committee discussed the manufacturer's assumption that the duration of aflibercept treatment was 1 year. The Committee heard from the clinical specialists that most patients still receive treatment with anti-VEGF therapy in year 2 and around a third of patients receive treatment in year 3. The clinical specialists also noted that data on the difference in the length of treatment with ranibizumab or aflibercept for macular oedema secondary to CRVO are not yet available. The Committee considered the manufacturer's scenario analyses in which the treatment duration of aflibercept was extended to 2 years or 4 years (see section 3.25) and the ERG's exploratory sensitivity analyses in which treatment duration was extended to 2 or 5 years and which included the confidential discount applied to the list price for aflibercept and a range of discounts from 0 to 50% applied to the list price of ranibizumab (see section 3.43). The Committee noted that when treatment duration was extended to 5 years, aflibercept was dominant over ranibizumab regardless of the discount applied to the ranibizumab

list price. The Committee concluded that the duration of aflibercept treatment was likely to be longer than 1 year, and that increasing the duration of treatment up to 5 years did not change the dominance of aflibercept over ranibizumab.

4.13 The Committee considered the source of health-related quality-of-life data used in the manufacturer's model. The Committee acknowledged that EQ-5D data from the European subset of the GALILEO population were used as a source of utility values in the manufacturer's base-case analysis, which meets NICE's reference case. The Committee also considered the manufacturer's scenario analyses, which used Czoski-Murray utility values, and included the confidential discount applied to the list price for aflibercept, noting that this did not affect the dominance of aflibercept over ranibizumab. The Committee noted that the ERG also carried out an exploratory sensitivity analysis using utility values from Czoski-Murray and Brown, which included the confidential discount applied to the list price for aflibercept and a range of discounts from 0 to 50% applied to the list price of ranibizumab. The Committee noted that the use of these utility values did not affect the dominance of aflibercept over ranibizumab unless there was a 50% reduction in the list price of ranibizumab. The Committee concluded that the source of the utility values did not substantially affect the cost-effectiveness estimates of aflibercept compared with ranibizumab.

4.14 The Committee considered how the cost of adverse events had not been included in the manufacturer' base-case analysis. It noted that the reason given in the manufacturer's submission was that anti-VEGFs have similar safety profiles to each other. The Committee also acknowledged that the manufacturer presented a scenario analysis that included adverse events and that adverse events were also included in the ERG's exploratory analyses (see

sections 3.25 and 3.43). The Committee noted that aflibercept continued to dominate ranibizumab in the manufacturer's scenario analysis and in the ERG's exploratory analysis if adverse events were included and a discount of 0 to 45% in the list price of ranibizumab was applied. The Committee was aware that the incremental cost-effectiveness ratio (ICER) for aflibercept was less than £3500 per QALY gained when a 50% discount was applied to the list price of ranibizumab. The Committee concluded that even if adverse events had been included in the manufacturer's base-case analysis, it was likely that aflibercept would continue to dominate ranibizumab.

4.15 The Committee discussed the fact that the manufacturer's model did not include a stopping rule. The Committee noted that the summary of product characteristics 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. It was also aware that the summary of product characteristics for ranibizumab for macular oedema secondary to retinal vein occlusion also states that continued treatment is not recommended if there is no improvement in visual acuity after 3 injections. The Committee heard from the clinical specialists that they would not continue treatment if there was no improvement in visual acuity after 3 injections. The Committee concluded that a stopping rule should have been included in the manufacturer's model.

4.16 The Committee discussed the administration costs of aflibercept and ranibizumab included in the manufacturer's model. The Committee noted that the manufacturer used a weighted average cost, based on the assumption that 52.38% of patients would be treated in an outpatient setting and the remaining in a day-case

setting. The Committee heard from the clinical specialists that most patients would be treated as outpatients; however, it also heard that not all units have the facilities to perform the treatment as an outpatient procedure. The Committee noted that the ERG presented lower costs of administration of aflibercept and ranibizumab in its report. The Committee concluded that the ERG's assumptions about the costs of administration were likely to be more realistic than those used by the manufacturer and therefore it was uncertain of the impact on the cost-effectiveness analyses.

4.17 The Committee discussed the costs of blindness included in the manufacturer's model. The Committee was aware that the source of the estimated costs of depression associated with blindness used by the ERG was more recent than the source used by the manufacturer. The Committee also noted that the costs of blindness presented by the ERG in their report were higher than those in the base-case analysis. The Committee recognised that if the costs presented by the ERG had been used, aflibercept would continue to dominate ranibizumab. The Committee concluded that the ERG's assumption about the costs of blindness were likely to be more in line with clinical practice than those used by the manufacturer.

4.18 The Committee considered ICERs for aflibercept compared with ranibizumab estimated by the manufacturer and the ERG. It noted that these analyses incorporated the discount agreed in the patient access scheme for aflibercept and a range of discounts applied to the list price of ranibizumab. The Committee was aware of the actual discount agreed in the patient access scheme for ranibizumab (this was submitted as commercial in confidence and therefore cannot be presented). It agreed that the analyses undertaken by the manufacturer and the ERG captured the

discount agreed in the patient access scheme for ranibizumab. The Committee noted that in the manufacturer's base-case analysis aflibercept dominated ranibizumab when the discounted price of aflibercept was used. The Committee considered the concerns raised by the ERG about the manufacturer's model and acknowledged the ERG's amendments to the manufacturer's model (see section 3.40). The Committee was aware that the ERG's exploratory analysis resulted in slightly more cost savings for aflibercept, and that aflibercept continued to dominate ranibizumab. The Committee also discussed the ERG's exploratory analysis around the list price of ranibizumab, incorporating the confidential discount on the list price for aflibercept. The Committee noted that a reduction of 0 to 45% in the list price of ranibizumab did not affect the dominance of aflibercept over ranibizumab. It also considered that when a 50% reduction was applied to the list price of ranibizumab, with the exception of the scenario of including the relative risk of losing 15 or more letters, the ICERs for aflibercept compared with ranibizumab ranged from £750 to £9300 per QALY gained. Taking into account the exact magnitude of the discounts agreed in the patient access schemes for aflibercept and ranibizumab, the Committee concluded that aflibercept was a cost-effective use of NHS resources compared with ranibizumab for treating people with visual impairment caused by macular oedema secondary to CRVO.

4.19 The Committee discussed the manufacturer's scenario analysis comparing aflibercept with dexamethasone, and the ERG's exploratory analyses. The Committee noted that the ERG's exploratory analysis, which included the confidential discount applied to the list price for aflibercept, resulted in an ICER of £12,300 per QALY gained for aflibercept compared with dexamethasone. The Committee considered that using Czoski-

Murray utility values resulted in an ICER of £12,900 per QALY gained and using Brown utility values resulted in an ICER of £16,800 per QALY gained when applied to the 'worse-seeing eye'. The Committee also acknowledged that even using the Brown utilities for the 'better-seeing eye', that is to say, the 'worst case scenario', the ICER was below the top end of the range that would normally be considered a cost-effective use of NHS resources (£20,000–30,000 per QALY gained). The Committee concluded that aflibercept was a cost-effective use of NHS resources compared with dexamethasone for treating people with visual impairment caused by macular oedema secondary to CRVO.

4.20 The Committee discussed how innovative aflibercept is in its potential to make a significant and substantial impact on health-related benefits. It agreed that aflibercept as well as other anti-VEGF treatments were a substantial improvement over previous treatments, and considered that this improvement applied to the class of drugs. In addition there were no substantial benefits of aflibercept over its comparators that were not already captured in the QALY estimation in the modelling.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion	Section
Key conclusion		
Aflibercept solution for injection is recommended as an option for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion only if the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme.		1.1
The clinical evidence from the COPERNICUS and GALILEO trials, which compared aflibercept with sham injection, showed that aflibercept was associated with a greater proportion of eyes gaining 15 or more letters from baseline to 24 weeks than sham injection.		4.6
The Committee accepted the results from the manufacturer's network meta-		3.10,

analysis. This showed that there is no statistically significant difference in the odds or relative risk of gaining 15 or more letters from baseline to 24 weeks for the comparison of aflibercept with ranibizumab, and that the odds and relative risk of gaining 15 or more letters from baseline to 24 weeks was statistically significantly smaller with dexamethasone compared with aflibercept.		4.7
The key driver for the cost-effectiveness results for the comparison of aflibercept with ranibizumab is the discount applied to the list price of ranibizumab. For the comparison of aflibercept with dexamethasone, the key driver is the source of the health-related quality of life data and whether it was applied to the 'worse-seeing eye' or 'better-seeing eye'.		4.18, 4.19
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard that visual impairment caused by macular oedema secondary to central retinal vein occlusion seriously impairs health-related quality of life.	4.2
	The Committee heard that the current standard treatment for macular oedema secondary to central retinal vein occlusion is dexamethasone or antivascular endothelial growth factor (anti-VEGF) drugs, such as ranibizumab. However, clinicians are more likely to use ranibizumab than dexamethasone because it is believed to have fewer side effects.	4.3
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee agreed that aflibercept as well as other anti-VEGF treatments were a substantial improvement over previous treatments, and considered that this improvement applied to the class of drugs. The Committee was not aware of any substantial benefits of aflibercept solution for injection over its comparators that were not already captured in the quality-adjusted life year (QALY) estimation in the modelling.	4.20
What is the position of the treatment in the pathway of care for the condition?	Aflibercept solution for injection has a UK marketing authorisation for 'the treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)'.	2.1

Adverse reactions	The Committee agreed that the evidence suggested the overall frequency of adverse events in the trials was low with aflibercept solution for injection and concluded that aflibercept had a similar adverse event profile to ranibizumab.	4.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee acknowledged that the evidence presented by the manufacturer was from 2 trials (COPERNICUS and GALILEO) and a network meta-analysis. The Committee was aware that the scope of the appraisal listed bevacizumab as a comparator. It noted that the manufacturer identified only 2 small trials of bevacizumab relevant to the network meta-analysis, and no trials that directly compared bevacizumab with aflibercept. The Committee concluded that there is currently not enough evidence to allow bevacizumab to be included with confidence in clinical and cost-effectiveness analyses.	4.4, 4.6, 4.7
Relevance to general clinical practice in the NHS	The Committee heard that the current standard treatment for visual impairment caused by macular oedema secondary to central retinal vein occlusion is dexamethasone or anti-VEGF drugs, such as ranibizumab.	4.3
Uncertainties generated by the evidence	The Committee heard from the clinical specialists and the Evidence Review Group (ERG) that different definitions of ischaemia and severe ischaemia exist. It concluded that it was unclear whether any evidence had been presented for people with ischaemia or severe ischaemia.	4.5
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	None	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee noted that aflibercept was associated with statistically significantly more eyes gaining 15 or more letters at 24 weeks compared with sham injection. The Committee concluded that aflibercept is a clinically effective treatment option for visual impairment caused by macular oedema secondary to central retinal vein occlusion.	4.6

Evidence for cost effectiveness		
Availability and nature of evidence	The Committee considered the manufacturer's economic model and the critique and exploratory analyses performed by the ERG. It accepted the model structure, but was concerned by some of the uncertainties about the assumptions used by the manufacturer.	4.9
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee considered the following uncertainties in the model: • the assumption that the benefits of treatment at 24 weeks would continue indefinitely • not including the relative risk of losing 15 or more letters • the assumption that the duration of aflibercept treatment was 1 year • the use of EQ-5D data as a source of utility values • not including the cost of adverse events • not including a stopping rule • overestimated administration costs for aflibercept and ranibizumab • underestimated costs of blindness. The Committee concluded that these uncertainties were unlikely to change the dominance of aflibercept over ranibizumab.	4.9-4.17
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee noted that the utility values in the manufacturer's base-case analysis were obtained from the EQ-5D data from GALILEO. The Committee heard from the ERG that using utility values from Czoski-Murray or Brown did not substantially affect the cost-effectiveness estimates of aflibercept compared with ranibizumab. The Committee was not aware of any substantial benefits of aflibercept over its comparators that were not already captured in the QALY estimation in the modelling.	4.13 4.20

Are there specific groups of people for whom the technology is particularly cost effective?	None	
What are the key drivers of cost effectiveness?	The manufacturer's sensitivity analyses showed that the cost effectiveness of aflibercept was sensitive to changes in the number of ranibizumab injections from 0 to 24 weeks and 25 to 52 weeks, the relative risk of gaining 15 or more letters when comparing aflibercept with ranibizumab, the number of aflibercept injections from 25 to 52 weeks, and the number of monitoring visits for ranibizumab from 0 to 52 weeks.	3.24
Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted that the manufacturer's base-case analysis showed that aflibercept dominated ranibizumab (that is, it was more effective and less costly), resulting in more QALYs and lower costs. The Committee considered the uncertainties in the manufacturer's model and noted the ERG's exploratory analysis, which resulted in slightly more cost savings with aflibercept. It also noted that aflibercept continued to dominate ranibizumab despite the changes made by the ERG. The Committee noted that the ERG's exploratory analysis, which included the confidential discount applied to the list price for aflibercept, resulted in an incremental cost-effectiveness ratio (ICER) of £12,300 per QALY gained for aflibercept compared with dexamethasone. The Committee also noted that even using the Brown utilities for the 'better-seeing eye', that is to say, the 'worst case scenario', the ICER was below the top end of the range that would normally be considered a cost-effective use of NHS resources (£20,000–30,000 per QALY gained).	4.18 4.19
Additional factors taken into account		
Patient access schemes (PPRS)	The Department of Health and the manufacturer have agreed that aflibercept will be available to the NHS with a patient access scheme which makes aflibercept available with a discount. The level of discount is commercial in confidence.	2.4

End-of-life considerations	Not applicable	
Equalities considerations and social value judgements	No equality issues relevant to the Committee's recommendation were raised.	

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has macular oedema secondary to central retinal vein occlusion and the doctor responsible for their care thinks that aflibercept is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 The Department of Health and the manufacturer have agreed that aflibercept will be available to the NHS with a patient access scheme which makes aflibercept available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]

5.4 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of publication. Further information is available on the NICE website.

- 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 secondary to retinal vein occlusion. NICE technology appraisal guidance 229 (2011).

7 Review of guidance

7.1 The guidance on this technology will be considered for review in February 2017. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Eugene Milne

Chair, Appraisal Committee

November 2013

8 Appraisal Committee members and NICE project team

8.1 Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne
Vice Chair of Appraisal Committee C, Director for Adult and Older Adult Health and Wellbeing, Public Health England

Dr Andrew Burnett
Formerly Director for Health Improvement and Medical Director, NHS Barnet, London

David Chandler
Lay Member

Gail Coster
Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome
Honorary Professor, Department of Primary Care and Population Health, University College London

Dr Greg Fell
Consultant in Public Health, Bradford Metropolitan Borough Council

Dr Wasim Hanif
Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

Dr Janice Kohler
Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital Trust

Emily Lam
Lay Member

Dr Nigel Langford
Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

Dr Allyson Lipp
Principal Lecturer, University of South Wales

Dr Claire McKenna
Research Fellow in Health Economics, University of York

Professor Gary McVeigh
Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Grant Maclaine
Formerly - Director, Health Economics & Outcomes Research, Becton, Dickinson and Company, Oxford

Dr Andrea Manca
Health Economist and Senior Research Fellow, University of York

Dr Paul Miller
Director, Payer Evidence, AstraZeneca UK Ltd

Professor Stephen O'Brien
Professor of Haematology, Newcastle University

Alan Rigby
Academic Reader, University of Hull

Professor Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Tim Stokes
Senior Clinical Lecturer, University of Birmingham

Dr Paul Tappenden
Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Dr Judith Wardle
Lay Member

Professor Robert Walton
Clinical Professor of Primary Medical Care, Barts and The London School of Medicine and Dentistry

8.2 NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ella Fields

Technical Lead

Nicola Hay/Dr Sally Doss

Technical Adviser

Lori Farrar

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Warwick Evidence:

- Shyangdan DS, Cummins E, Clar C et al. Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion – a single technology assessment. October 2013

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on aflibercept solution for injection for the treatment of macular oedema caused by central retinal vein occlusion by providing a written statement to the Committee. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

I. Manufacturer/sponsor

- Bayer

II. Professional/specialist and patient/carer groups:

- Macular Society
- Organisation of Blind African Caribbeans
- Royal College of Nursing
- Royal College of Ophthalmologists
- Royal College of Pathologists
- Royal National Institute of Blind People (RNIB)
- South Asian Health Foundation

III. Other consultees:

- Department of Health

- NHS Coventry and Rugby Clinical Commissioning Group
- NHS Enfield Clinical Commissioning Group
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Allergan
- Cochrane Eyes and Vision Group
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- National Institute for Health Research Health Technology Assessment Programme
- Novartis Pharmaceuticals
- Roche Products
- Warwick Evidence

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on aflibercept solution for injection for the treatment of macular oedema caused by central retinal vein occlusion by providing oral evidence to the Committee.

- Ian Pearce, Consultant Ophthalmologist, nominated by Bayer – clinical specialist
- Sobha Sivaprasad, Consultant Ophthalmologist, nominated by Royal College of Ophthalmologists – clinical specialist
- Cathy Yelf, Head External Relations, nominated by Macular Society – patient expert
- Clara Eaglen, Policy and Campaigns Manager, nominated by RNIB – patient expert

D. Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Bayer