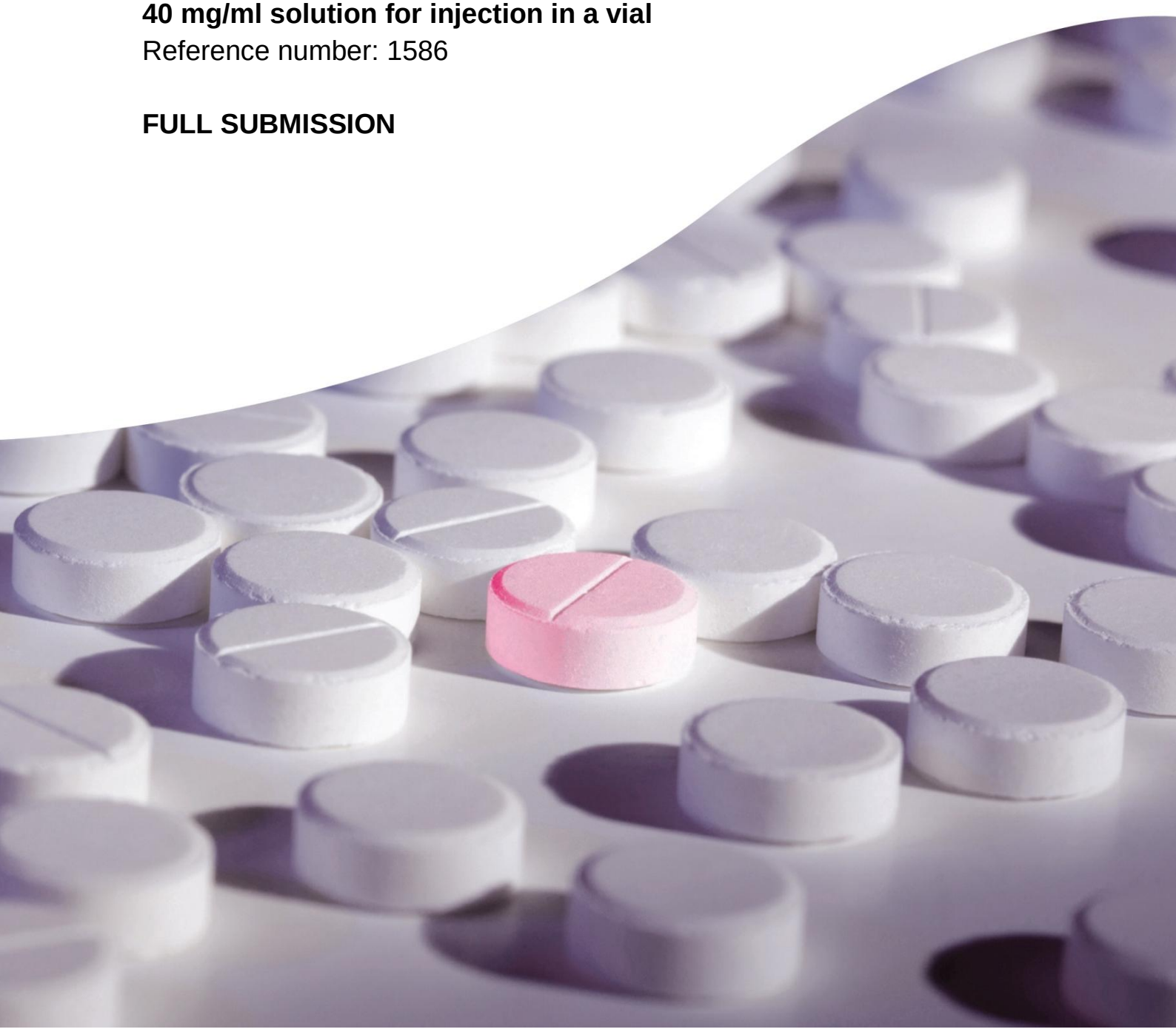
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Aflibercept (Eylea®)
40 mg/ml solution for injection in a vial
Reference number: 1586

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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This report should be cited as:
All Wales Therapeutics & Toxicology Centre. AWMSG Secretariat Assessment Report. Aflibercept (Eylea®) 40 mg/ml solution for injection in a vial. Reference number: 1586. January 2017.

AWMSG Secretariat Assessment Report
Aflibercept (Eylea®▼) 40 mg/ml solution for injection in a vial

This assessment report is based on evidence submitted by Bayer plc[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Aflibercept (Eylea®▼) for treatment of adult patients with visual impairment due to myopic choroidal neovascularisation[2]. Refer to the Summary of Product Characteristics for the full licensed indication[2]. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
Dosing	Aflibercept (Eylea®) is for intravitreal injection only. The recommended dose is a single intravitreal injection of 2 mg aflibercept, equivalent to 50 microlitres. Additional doses may be administered if the disease persists. The interval between two doses should not be shorter than one month. Refer to the Summary of Product Characteristics for further information[2].
Marketing authorisation date	Date of licence extension 28 October 2015 (licensed for original indication on 22 November 2012)[2].
UK launch date	Planned Q3/Q4 2016[1]

2.0 DECISION CONTEXT

2.1 Background

Myopic choroidal neovascularisation (mCNV) refers to the development of choroidal neovascularisation (growth of abnormal blood vessels under the retinal pigment epithelium or retina) in patients with pathological myopia[3]. Choroidal neovascularisation is a frequent complication of pathological myopia and is a sight-threatening condition[3]. Without treatment, approximately 90% of patients will be severely sight impaired (visual acuity less than 20/200) five years after the onset of mCNV[4]. Younger individuals are typically affected by mCNV, occurring approximately a decade earlier than other common blinding eye diseases and carrying a greater socioeconomic impact[5].

Treatment choices for mCNV have included photocoagulation[6,7] and verteporfin photodynamic therapy (vPDT), which can prevent further loss of vision but do not improve visual acuity[8,9]. More recently, intravitreal vascular endothelial growth factor (VEGF) inhibitors have demonstrated an improvement in mean visual acuity following successful treatment of mCNV[10]. Inactivation of VEGF is thought to inhibit the growth of abnormal blood vessels[11]. Ranibizumab, a VEGF-A inhibitor, was recommended by the National Institute for Health and Care Excellence (NICE) as an option for the treatment of visual impairment due to mCNV in 2013[12].

Aflibercept is a novel recombinant fusion protein that inhibits all isoforms of VEGF-A and placental growth factor (another VEGF)[11]. The company propose aflibercept as a first line option for the management of visual impairment due to mCNV[1].

2.2 Comparator
The comparator included in the company submission was ranibizumab[1].

2.3 Guidance and related advice
- NICE. Technology Appraisal Guidance, TA298. Ranibizumab for treating choroidal neovascularisation associated with pathological myopia (2013)[12].
- The All Wales Medicines Strategy Group (AWMSG) has previously issued a Statement of Advice for the use of aflibercept (Eylea®) for the treatment of adults with visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)[13]. Aflibercept is recommended by NICE as an option for treatment of the original licensed indications (macular oedema after branch or central retinal vein occlusion, diabetic macular oedema and wet age-related macular degeneration)[14-17].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes a pivotal phase III, multicentre, randomised, double-masked, sham-controlled study (MYRROR) to assess the efficacy and safety of intravitreal aflibercept compared with sham treatments in patients with mCNV[1]. In the absence of any head-to-head trials between aflibercept and its comparator treatments in mCNV, a systematic literature review and indirect treatment comparison (ITC) was conducted to derive comparative treatment efficacy estimates[1].

3.1.1 MYRROR study
In the MYRROR study 122 patients were randomised in a 3:1 ratio to intravitreal aflibercept or sham treatment for 24 weeks[1,18]. At week 24 patients in the sham group were switched to aflibercept treatment. From baseline to week 24 patients in the active treatment arm received one 2 mg aflibercept intravitreal injection at baseline followed by as needed dosing of aflibercept in accordance with specific retreatment criteria, at a maximum of once every four weeks. Retreatment was allowed in patients who met one or more of the following criteria: (1) reduction in visual acuity by ≥ 5 letters from the previous Early Treatment Diabetic Retinopathy Study (ETDRS) examination; (2) increase in central retinal thickness > 50 micrometres from the time of the previous examination, new or persistent cystic retinal changes, subretinal fluid, or pigment epithelial detachment, and new or persistent CNV or bleeding; or (3) deemed necessary by the investigator based on his/her clinical impression or diagnostics performed in the context of standard medical care. Patients received sham injection for masking purposes when patients were assessed as not needing retreatment. Patients in the sham control group received one sham injection at baseline followed by repeated sham injections every four weeks through to week 20. From weeks 24 to 48 the aflibercept group continued as needed dosing of aflibercept or sham injection in accordance with the same retreatment criteria. Patients in the control group received one 2 mg aflibercept injection at week 24 followed by as needed dosing of 2 mg aflibercept or sham injection, once every four weeks[1,18]. All patients were of Asian ethnicity, aged ≥ 18 years with high myopia and active mCNV. Exclusion criteria included a history of CNV with an origin other than pathologic myopia in the study eye and recurrent mCNV[1,18].

The primary endpoint was mean change from baseline in best-corrected visual acuity (BCVA) measured by ETDRS letter score at week 24[1,18]. Baseline BCVA was comparable between the two groups. At week 24 patients in the aflibercept treatment group had clinically relevant[19,20] improved BCVA scores compared with the sham group (mean change of +12.1 letters compared with -2.0 letters, respectively); results are shown in Table 1[1,18]. Superiority of aflibercept over sham treatment was confirmed by analysis of the key secondary endpoint; 38.9% (n = 35) and 9.7% (n = 3) of patients

respectively had a clinically meaningful gain of 15 or more letters (p = 0.0001) during the first 24 weeks of the study[1,18,19]. Results of additional vision endpoints (mean change in BCVA and proportion of patients gaining 15 or more letters at week 48, and proportion of patients gaining 10 or more letters at weeks 24 and 48) suggested that delayed treatment with aflibercept may be less beneficial[1,18,19]. Anatomical exploratory endpoints (change from baseline in central retinal thickness, change from baseline in CNV lesion size and change from baseline in area of leakage, all measured at 24 and 48 weeks) were generally supportive of the primary and key secondary endpoints[1,18,19].

Table 1. Mean change in BCVA from baseline to week 24[1,18]

Treatment	Aflibercept* N = 90	Sham N = 31
Mean BCVA (SD) at baseline	56.4 (9.8)	56.6 (8.9)
Mean BCVA (SD) at week 24	68.5 (10.8)	54.6 (9.8)
Mean change from baseline to week 24 (letter score)	12.1	-2.0
LS mean change (letter score)	13.2	-0.9
Difference in LS mean changes at week 24† (95% CI), p-value	14.1(10.8-17.4) < 0.0001	

BCVA: best-corrected visual acuity; CI: confidence interval; LS: least squares; SD: standard deviation; *Aflibercept administered at baseline and every 4 weeks as needed in the event of disease recurrence. † Point estimate, 95% CI and p-value are based on treatment difference (aflibercept minus sham) in LS mean changes, using an analysis of covariance (ANCOVA) model with treatment group and country (country designations) as fixed effects. Baseline value of BCVA was included in the model.

Vision-related quality of life was assessed using the National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25) and overall health status was assessed using the EuroQol-5 Dimension (EQ-5D) score[1,18]. Both were assessed using last observation carried forward (LOCF) and observed case (OC) approaches. A small but statistically significant increase from baseline at week 24 was observed in NEI VFQ-25 scores in the aflibercept group compared with a slight decrease in the sham group using LOCF, but this was not replicated using the OC approach. [Academic in confidence text removed]. No significant difference was observed in total EQ-5D score at week 24 using either LOCF or OC, however significant improvements were observed using both approaches in the mean change from baseline at week 48 in the aflibercept group compared with sham/aflibercept[1,18].

In the aflibercept group 14.4% of patients only required one injection in the 48–week study period, with 58.9% requiring no more than three injections[1]. The mean number of active injections needed in the aflibercept and sham/aflibercept arms over the study duration was 4.2 and 3.0 respectively[18], with increased numbers of injections being administered in the first 12 weeks of the aflibercept arm[1].

3.1.2 Indirect comparison of aflibercept with comparator treatments

In the absence of trials directly comparing the clinical effectiveness of aflibercept with relevant comparators the company estimated comparative efficacy from an ITC[1]. A systematic literature review identified three relevant randomised control trials (RCTs) which were used to create an evidence network. Study inclusion criteria were RCTs in which patients with mCNV were treated with aflibercept (MYRROR[18]), ranibizumab (RADIANCE[21]) or vPDT (RADIANCE and VIP[8,21]). Baseline patient demographics were reasonably balanced across all three studies with the exception of racial distribution. The MYRROR study[18] was conducted in an East Asian population exclusively, in contrast with the VIP and RADIANCE studies[8,21] where 91% and 56.6% of patients

respectively were Caucasian. The reported primary outcome was the mean change in BCVA. Due to treatment switching at fixed endpoints the only common time period for which BCVA gain was available between all studies was 13 weeks. The ITC results of the 13 week mean BCVA change show that aflibercept and ranibizumab have similar efficacy and both demonstrate significant improvements over placebo and vPDT[1] (see Table 2).

Table 2. ITC results for mean 13 week gain in BCVA[1]

	Mean BCVA at 13 weeks	SD	95% CI low	95% CI high
Aflibercept versus placebo	13.09	2.04	9.10	17.08
Aflibercept versus vPDT	12.04	3.05	6.10	18.00
Aflibercept versus ranibizumab (vision*)	1.34	3.40	-5.35	8.00
Aflibercept versus ranibizumab (disease*)	0.94	3.38	-5.67	7.56
vPDT versus placebo	1.05	2.29	-3.47	5.50
Ranibizumab (vision*) versus placebo	11.75	2.75	6.31	17.09
Ranibizumab (disease*) versus placebo	12.15	2.72	6.76	17.43

BCVA: Best Corrected Visual Acuity; SD: standard deviation; CI: credible interval; vPDT: verteporfin photodynamic therapy
* Patients were randomised to two treatment groups in the RADIANCE study; after initial ranibizumab treatment further treatment was determined by either visual acuity stabilisation (vision) or disease activity (disease) criteria depending on group allocation.

3.1.3 Safety

There are no direct or indirect comparative safety data comparing aflibercept with ranibizumab. In the MYRROR study the proportion of patients experiencing at least one treatment-emergent adverse event (TEAE) over the 48 week study period was 67.2% (70.3% and 58.1% in the aflibercept and sham/aflibercept groups respectively); this difference was mainly due to non-ocular TEAEs[1,18,19]. Four subjects experienced a non-ocular TEAE considered to be related to the study drug (three [3.3%] in the aflibercept group and one [3.2%] in the sham/aflibercept group)[1,18,19].

Ocular TEAEs in the study eye occurred in 31.9% and 35.5% of patients in the aflibercept and sham/aflibercept groups respectively, of which 6.6% (aflibercept) and 3.2% (sham/aflibercept) were considered to be related to the study drug[1,18,19]. The most frequently reported ocular TEAEs through week 48 were conjunctival haemorrhage (11.0%), eye pain (7.7%) and punctate keratitis (6.6%) in the aflibercept group and punctate keratitis (12.9%), dry eye (6.5%) and posterior capsule opacification (6.5%) in the sham/aflibercept group. Most ocular TEAEs were mild or moderate in severity with one ocular TEAE (macular hole) in the aflibercept group assessed as severe and the only treatment-, procedure- or injection- related serious adverse event. Procedure-related TEAEs occurred exclusively in the aflibercept group and injection-related TEAEs were reported slightly more frequently in the aflibercept group (20%) compared with the aflibercept/sham group (13%) [1,18,19].

A total of five patients discontinued aflibercept treatment due to TEAEs before week 48; four from the aflibercept group (idiopathic thrombocytopenic purpura, cerebral haemorrhage, mild CNV in the fellow eye and mild abnormal hepatic function) and one from the sham/aflibercept group (impetigo)[1,18,19]. In an evaluation of ethnical insensitivity the company pooled safety data from the previous trials in existing

aflibercept indications; there was no indication that intrinsic or extrinsic factors would cause differences in safety between ethnic subgroups[22-24].

Overall, the Committee for Medicinal Products for Human Use (CHMP) considered the safety profile in patients with mCNV to be generally consistent with the known safety profile in the other licensed indications, but have asked for close monitoring of cerebral haemorrhage, hypertension and macular hole in periodic safety update reports[19].

3.2 AWTTC critique

- The company consider ranibizumab as the most appropriate comparator stating that it is considered to be standard of care for patients with mCNV in Wales. This is based on a company conducted survey of 52 UK ophthalmologists, however only two of the 52 clinicians surveyed were practising in Wales[1]. Ranibizumab is the only other VEGF inhibitor licensed in the UK for the treatment of mCNV and is recommended as a possible treatment for this indication by NICE[12]. Clinical expert opinion sought by AWTTC confirms that ranibizumab is the most appropriate comparator.
- There are no head-to-head studies comparing aflibercept with ranibizumab and an ITC was therefore conducted[1]. While a common approach to the lack of direct head-to-head comparison data, an indirect comparison has inherent limitations. Uncertainties and assumptions in the ITC include: a weighted average of the 12 week and 16 week outcomes was required from the MYRROR dataset to allow comparisons to be made with three month data from the RADIANCE and VIP studies; no standard deviation (SD) was reported for the three month BCVA in both ranibizumab arms in RADIANCE so it was assumed that this was equal to the SD for the mean difference of BCVA versus baseline over all monthly assessments from month one to month three; the VIP study presented median BCVA gain and consequently no SD was reported; vision gain is normally distributed thereby implying parity between the mean and median[1]. Any conclusions drawn from the ITC should be interpreted with caution.
- No direct or indirect comparative safety data are available for aflibercept and ranibizumab. The safety profile of aflibercept in the treatment of mCNV was considered to be consistent with that previously reported in other target populations[1,19]. The limited population size in the MYRROR study may have precluded detection of rare adverse events and there are no clinical or safety data generated beyond one year. CHMP recommend that mCNV patients are included in the post-authorisation risk management plan[1,19].
- The MYRROR study was conducted in Asian patients. An evaluation of the ethnical insensitivity was conducted by the applicant company[1,19]. Based on the results of this analysis, CHMP considered extrapolation of the MYRROR study results to the European population to be acceptable[19].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission includes a cost-minimisation analysis (CMA) of 2 mg aflibercept as an alternative first line treatment option to 0.5 mg ranibizumab (both given as a single intravitreal injection) in adult patients with visual impairment due to mCNV[1].

Ranibizumab is the only comparator and is reported to be the standard of care for 74% of treated mCNV patients, based on the results of a market research survey carried out by the company in January 2016[1]. The remaining 26% of current utilisation was found to be: 10% aflibercept, 9% unlicensed bevacizumab, 2% vPDT and 5% no treatment

given. The economic evaluation did not consider comparison to bevacizumab, vPDT or 'no treatment'.

As no study data were available for aflibercept compared to ranibizumab, an ITC, as described in section 3.1.2, was conducted for the primary outcome of mean change in BCVA and was provided as evidence of equivalence in clinical efficacy. According to the ITC, at 13 weeks aflibercept was estimated to improve vision by 0.94 and 1.34 letters against the RADIANCE disease-guided retreatment and vision-guided retreatment arms, respectively. The credible intervals between aflibercept and ranibizumab (disease and vision outcomes) overlap. Evidence reported in the submission suggests that at least a ten letter change in vision must occur before significant functional changes in health-related quality of life (HRQoL) are observed and therefore equivalence was assumed for the two treatments[20]. Safety outcomes and other secondary clinical outcomes were not included in the network of evidence and were not included in the cost-minimisation analysis.

Medicine acquisition costs were included in the model. The list prices for aflibercept and ranibizumab are £816 and £551 per vial, respectively[25]. The confidential Patient Access Scheme (PAS) available for aflibercept gives a price of [commercial in confidence data removed]. A confidential PAS is also available for ranibizumab. A two-year treatment duration was assumed, with 4.20 injections in year one and 1 injection in year two for both treatments. The injection frequency was based on the MYRROR study. Vision related costs, monitoring costs, adverse event costs, administration costs and discontinuation of treatment were not included in the model.

The perspective was the NHS in Wales and personal social services (PSS). A discount rate of 3.5% was applied beyond year one and rates of 0% and 6% were tested in a sensitivity analysis. An annual cycle length was used in the model. Fellow-eye involvement (FEI) and future disease recurrence were considered and assumed equal for both treatments.

The time horizon was lifetime as mCNV is a chronic condition. The baseline age for the modelled population was 58 years and 76% of patients were female, based on the population in the MYRROR study. The overall patient population considered in the analysis also reflects the indication for aflibercept for mCNV in the MYRROR study, including patients aged ≥ 18 years, with a visual impairment due to mCNV, and a BCVA of between 73 and 35 letters (inclusive).

4.1.2 Results

The base case model reports the cost difference over a patient's lifetime with the PAS discount applied to aflibercept and the list price of ranibizumab (see Table 3). The estimated life expectancy in the model was 25.25 years for patients with mCNV.

The results of the CMA indicate that aflibercept is the cost-saving option when the PAS discount is applied, compared to ranibizumab list price with no discount applied, [commercial in confidence data removed] versus [commercial in confidence data removed] respectively.

Table 3. Results of the base case analyses

Base-case analysis	Aflibercept (including PAS discount)	Ranibizumab (list price)	Difference
First eye: Initial treatment	¶¶	£2,828	¶¶
First eye: Recurrence treatment	¶¶	¶¶	¶¶
Fellow-eye: Initial treatment	¶¶	¶¶	¶¶
Fellow-eye: Recurrence treatment	¶¶	¶¶	¶¶
Total cost (discounted)	¶¶	¶¶	¶¶

PAS: patient access scheme

¶¶ commercial in confidence figure removed

As ranibizumab has a PAS discount the most appropriate results for consideration are from an additional sensitivity analysis requested comparing aflibercept (with PAS discount) versus ranibizumab at various discount rates between 0% and 50% of list price (see Table 4).

Parity in cost is achieved when ranibizumab has a discount of [commercial in confidence data removed] when compared to the discounted aflibercept price ([commercial in confidence data removed] discount in line with the current PAS). Aflibercept is cost saving if the discount on ranibizumab is lower than [commercial in confidence data removed]. If the discount on ranibizumab is above [commercial in confidence data removed] ranibizumab is cost-saving.

Table 4. Sensitivity analyses of various discount rates applied to ranibizumab compared to aflibercept with PAS discount ([commercial in confidence data removed])

Discount applied to ranibizumab	Ranibizumab cost	Cost difference
5%	¶¶	¶¶
10%	¶¶	¶¶
15%	¶¶	¶¶
20%	¶¶	¶¶
25%	¶¶	¶¶
30%	¶¶	¶¶
35%	¶¶	¶¶
40%	¶¶	¶¶
45%	¶¶	¶¶
50%	¶¶	¶¶

¶¶ commercial in confidence figure removed

The company submitted further sensitivity analyses for recurrence rate, FEI rate, and number of injections given for a recurrence. The sensitivity analyses for recurrence rates have the greatest impact on the results. If the recurrence rate is higher than the baseline [academic in confidence data removed] then the incremental savings increase for aflibercept (PAS discount) compared to ranibizumab (list price). If the recurrence rate is lower (6% as used in the NICE technology appraisal for ranibizumab) then the incremental savings decrease for aflibercept (PAS discount) compared to ranibizumab (list price). Table 5 details these analyses together with an exploration of their plausibility.

Table 5. Additional sensitivity analyses

Scenario	Discounted incremental lifetime cost for aflibercept (PAS) and ranibizumab (list)	Discounted incremental lifetime cost for aflibercept (list) and ranibizumab (list)	Plausibility
Base case	-£2,540	¶¶	Recurrence rate in the base case [academic in confidence data removed] was based on clinical opinion from company market research.
Recurrence rate			
36% recurrence rate	¶¶	¶¶	Alternative recurrence rate based on the VIP study (vPDT arm)[8].
54% recurrence rate	¶¶	¶¶	Alternative recurrence rate based on the VIP study (placebo arm)[8]
6% recurrence rate	¶¶	¶¶	Alternative recurrence rate based on manufacturer's estimated recurrence rate in the NICE ranibizumab submission[12].
Recurrence injection rate			
First year injection rate increased by 25%	¶¶	¶¶	Pragmatic variation provided by the company.
First year injection rate decreased by 25%	¶¶	¶¶	Pragmatic variation provided by the company.
FEI rate			
[Academic in confidence data removed] FEI rate increased by 25%	¶¶	¶¶	Pragmatic variation provided by the company.
[Academic in confidence data removed] FEI rate decreased by 25%	¶¶	¶¶	Pragmatic variation provided by the company.

FEI: fellow eye involvement; PAS: patient access scheme; vPDT: verteporfin photodynamic therapy
¶¶ commercial in confidence figure removed

4.1.3 AWTTC critique

The company have submitted a CMA; however, the rationale to support this approach does not in this case meet with AWTTC guidance for use of CMA as the form of pharmacoeconomic evaluation.

Strengths of the economic analysis include:

- The company has submitted a simple, transparent analysis.
- Clear description of the inputs and exclusions has been provided.
- A range of sensitivity analyses have been performed to examine the impact of varying the values of key input parameters.

Limitations of the economic analysis include:

- The company acknowledge that a cost-utility analysis (CUA) is the preferred choice of economic evaluation and give the reason for choosing a CMA as a high degree of similarity between the drugs for comparison, as well as a large degree of uncertainty surrounding treatment effects. However, this approach does not meet with AWTTC guidance for use of CMA as the form of economic evaluation.
- The suggestion that the CMA approach is conservative is not supported by the evidence. The very small difference in efficacy reported in the ITC is not likely to bias against aflibercept, especially given the uncertainty surrounding the efficacy comparison as described in section 3.2.
- Ranibizumab is the only comparator and is reported to be the standard of care for 74% of treated mCNV patients. It may have been appropriate to account for bevacizumab, vPDT and 'no treatment' in the economic evaluation[1]; however, the economic evaluation did not take these into account. The company acknowledged that 'no treatment' was not considered a relevant comparator as these patients were likely to be ineligible or had chosen not to receive anti-VEGF treatment and highlighted that bevacizumab it not licensed for the treatment of mCNV[12].
- The model assumes the same retreatment rates for both aflibercept and ranibizumab but the protocols for retreatment in the MYRROR and RADIANCE studies were different. In the MYRROR and RADIANCE studies the mean number of injections in year one for aflibercept was fewer than ranibizumab when retreatment was based on visual acuity; when retreatment was based on disease progression ranibizumab had fewer injections in year one. The applicant company suggest that this difference impacts the comparability of the efficacy estimates and injection frequency.
- The company's market research suggests that clinicians expect to administer less than half the number of aflibercept injections than ranibizumab injections, however these results are based on current treatment practice where 74% of patients receive ranibizumab and only 10% receive aflibercept. Analysis of the market research data indicates that the survey results appear to be questionable.
- Adverse events have not been included in the model as they have been assumed to be equivalent between treatments; this assumption is based on medical opinion. There are no direct or indirect comparative safety data, though the company highlight that results from head-to-head trials between aflibercept and ranibizumab in other eye conditions (diabetic macular oedema and wet age-related macular degeneration) and a European Medicines Agency assessment of aflibercept for wet age-related macular degeneration indicate that the safety profile of aflibercept appears to be similar to ranibizumab[22,26,27]. Adverse events can result in the need for additional treatments and decreases in quality of life and should be included within the economic evaluation if there is a clinically meaningful difference between the two treatments.
- A lifetime horizon was used in the model and it would be expected that eyesight would slowly deteriorate over that time. Deterioration due to natural disease progression was not considered in the model as no evidence was identified to suggest any difference between the compared treatments, though the company acknowledged uncertainty and a lack of data associated with modelling visual outcomes over long periods of time.

4.2 Review of published evidence on cost-effectiveness

One cost-effectiveness evaluation abstract was identified[28], but full details of the evaluation are not reported. Ranibizumab was compared to aflibercept in a UK setting.

The evaluation was based on the RADIANCE and MYRROR studies, and relative efficacy was assessed by indirect comparison. The results of the evaluation found ranibizumab dominated aflibercept, with a lower lifetime cost and higher lifetime quality-adjusted life years. The results were driven by a greater number of injections, higher treatment and recurrence costs, and a smaller proportion of patients gaining ≥ 20 letters visual acuity for aflibercept. The company responded that in this CUA the efficacy parameters were estimated from the disease activity treatment arm of the RADIANCE study only, the ITC did not adjust for underlying baseline characteristics that may interact with the treatment effect and that list prices (as at 2014) rather than PAS prices were used for both aflibercept and ranibizumab.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

No Wales specific prevalence rates of mCNV patients were identified. The population projection for Wales was 3,092,000 (2014 projection), of which 40.6% are aged 49 years or older[29]. A prevalence rate for pathologic myopia in patients aged 49 years or older of 1.2% was identified[30]. Using estimates from three studies mCNV was estimated to be prevalent in 5.2% to 11.3% of patients suffering from pathologic myopia[31-33]. The lower bound estimate was used because this came from studies conducted in the United States, which was considered more reflective of a Western European population.

A correction factor of 1.32 was applied to expand the population to include patients less than 49 years of age. This was based on the proportion of mCNV patients less than 49 years of age included in the MYRROR study[18].

The company estimated that 1,037 people currently suffer from mCNV in Wales.

Using an annual incidence rate of 1.45%, 290 people in Wales will develop mCNV per year[34]. The estimated diagnosis rate was 85%, and an estimated 81% patients would be eligible for pharmacotherapy resulting in 199 patients eligible for aflibercept per year. It is then assumed that 80% of patients eligible for treatment will start treatment per year, i.e. 160 patients. The market share was assumed to be [commercial in confidence data removed] in the first year and [commercial in confidence data removed] in subsequent years. This means that [commercial in confidence data removed] patients are assumed to receive aflibercept in year one, [commercial in confidence data removed] in year two, and [commercial in confidence data removed] in each subsequent year. Assuming [academic in confidence data removed] of patients will present with FEI at the start of treatment increases the number of eyes treated per year to [commercial in confidence data removed] in year one, [commercial in confidence data removed] in year two, and [commercial in confidence data removed] in each subsequent year. Assuming a [academic in confidence data removed] recurrence rate leads to [commercial in confidence data removed] and [commercial in confidence data removed] additional eyes in years three, four and five respectively.

5.1.2 Results

The budget impact analysis indicates an initial saving in year one of [commercial in confidence data removed], increasing to a saving of [commercial in confidence data removed] in year five; however this is a comparison of aflibercept with the PAS discount of [commercial in confidence data removed] compared to the list price of ranibizumab which would not occur in practice in Wales as both treatments have a PAS discount. A sensitivity analysis of the discount applied to ranibizumab was reported for discounts of 0% to 50% compared to aflibercept discounted at [commercial in confidence data removed] (see Table 6 and Table 7). Aflibercept is potentially cost

saving when the discount applied to ranibizumab is [commercial in confidence data removed]. The plausibility of the scenarios in Table 7 depends on the discount agreement for ranibizumab.

Table 6. Company-reported figures associated with use of aflibercept for the treatment of mCNV in adults

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Number of eligible patients (Indication covered in this submission)	160	319	479	638	798
Uptake (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Estimated number of initial treated eyes	¶¶	¶¶	¶¶	¶¶	¶¶
Estimated number of recurrence treated eyes			¶¶	¶¶	¶¶
Discontinuation rate	Not applied in the model				
Net cost	¶¶	¶¶	¶¶	¶¶	¶¶
Cumulative net cost	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ commercial in confidence figure removed					

Table 7. Sensitivity analyses of various discount rates applied to ranibizumab compared to aflibercept with PAS discount ([commercial in confidence data removed])

Scenario	Net financial costs or savings at five years
Base case	¶¶
5% discount	¶¶
10% discount	¶¶
15% discount	¶¶
20% discount	¶¶
25% discount	¶¶
30% discount	¶¶
35% discount	¶¶
40% discount	¶¶
45% discount	¶¶
50% discount	¶¶
¶¶ commercial in confidence figure removed	

The company submitted further sensitivity analyses for recurrence rate, FEI rate, and number of injections given for a recurrence. The sensitivity analyses for recurrence rates have the greatest impact on the results. If the recurrence rate is higher than the baseline ([academic in confidence data removed]) then the incremental savings increase for aflibercept (PAS discount) compared to ranibizumab (list price). If the recurrence rate is lower (6% as used in the NICE TA for ranibizumab) then the incremental savings decrease for aflibercept (PAS discount) compared to ranibizumab (list price).

5.1.3 AWTTC critique

- No sensitivity analyses are presented for percentage of patients diagnosed, patients eligible for pharmacotherapy, recurrence rate, FEI rate, treatment for recurrence, or treatment for FEI. These parameters are likely to have an impact on the budget required for treatment of mCNV in Wales.
- The estimate for prevalence of mCNV in patients suffering from pathologic myopia is taken from two very dated United States studies (1970 and 1992), chosen because the United States population was assumed to be more representative of a Western European population than other more recent studies in Japanese patients. No evidence is provided in the submission as to whether the prevalence of mCNV has changed significantly since 1992.

5.2 Comparative unit costs

Table 7. Examples of acquisition costs of licensed treatments for mCNV

Medicine	Example doses	Unit	Approximate costs per dose per patient with no PAS
Aflibercept (Eylea®)	Single 2 mg intravitreal injection* (equivalent to 50 microlitres of aflibercept solution for injection)	40 mg/ml solution for injection (0.1 ml vial)	£816
Ranibizumab (Lucentis®)	Single 500 microgram intravitreal injection*	10 mg/ml solution for injection (0.23 ml vial)	£551
vPDT	6 mg/m^2 intravenous infusion over 10 minutes	injection, powder for reconstitution (15 mg vial)	£850

vPDT: verteporfin photodynamic therapy; PAS: Patient Access Scheme
*Additional doses may be administered at monthly intervals if the disease persists[2,35]
Costs are based on BNF list prices as of October 2016, assuming vial wastage[25].
Costs of administration are not included.
This table does not imply therapeutic equivalence of medicines or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, aflibercept (Eylea®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that aflibercept (Eylea®) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months[1].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 16 September 2016
Date range of evidence search: No date limits were applied to database searches.

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