**London Medicines Evaluation Network Review**

**Aflibercept in Diabetic Macular Oedema (DMO)**

**April 2015**

### Summary

**Background and licensed indication**
Eylea® (aflibercept 2mg intravitreal injection) has been available since 2012 with Marketing Authorisation for the treatment of adults with visual impairment due to Wet Age Related Macular Degeneration (AMD) or Macular Oedema following Central Retinal Vein Occlusion (CRVO). In August 2014 the European Union’s Committee for Medicinal Products for Human Use (CHMP) recommended extending the Marketing Authorisation for Eylea® to treat adult patients with vision loss due to diabetic macular oedema (DMO).

**Dosing**
The recommended dose for Eylea® is 2 mg, initiated with one injection per month for five consecutive doses, followed by one injection every two months for 12 months. After the first 12 months, the treatment interval may be extended based on visual and anatomic outcomes.

**Alternatives**
Alternatives are dependent on local pathways in place or being developed for DMO. They may include:
- Ranibizumab (Lucentis®) or bevacizumab (off-label use)
- Laser photocoagulation
- Intravitreal steroid implants such as Iluvien® (fluocinolone acetonide) or Ozurdex® (dexamethasone)

**NICE**
- A NICE TA on aflibercept intravitreal injection for DMO is expected in June 2015. NICE (TA 274) recommends ranibizumab (Lucentis®) as an option for treating visual impairment due to DMO if the eye has a central retinal thickness of ≥ 400 micrometres (µm) at the start of treatment.
- NICE (TA 301) recommends flucinolone acetonide intravitreal implant (Iluvien®) for patients with DMO unresponsive to other treatment options and with an artificial lens. A NICE TA on Ozurdex® (dexamethasone intravitreal implant) is due in June 2015.
- Both ranibizumab and flucinolone acetonide were approved by NICE on the condition that an approved aflibercept may offer a cost benefit assuming no further monitoring visits are required in addition to treatment visits.

**Clinical studies**
Aflibercept was evaluated for the treatment of DMO in three large studies (VISTA-DME, VIVID-DME and the DA VINCI study) against laser photocoagulation therapy. At the licensed dose, aflibercept was superior to laser therapy (given up to every 12 weeks in VISTA-DME/VIVID-DME or up to every 16 weeks in DA VINCI) at 52 weeks with the possibility that effectiveness continues for up to 2 years with as-needed dosing. Efficacy beyond two years will be established with longer term studies which are still on-going. There are no direct comparison studies of aflibercept with ranibizumab in patients with DMO but independent comparison studies are available and these suggest similar efficacy. Subgroup analysis suggested that patients with DMO who have tried other VEGF inhibitors may benefit from aflibercept as well as those who are naïve to intravitreal VEGF inhibitor treatment.

**Safety**
Incidence of conjunctival haemorrhage, eye pain, ocular hyperaemia and vitreous floaters and systemic adverse effects were similar for aflibercept and laser photocoagulation therapy in VISTA-DME and VIVID-DME. Endophthalmitis and transient raised intraocular pressure were observed in patients given aflibercept in the DA VINCI study. Indirect studies suggest comparable tolerability compared with intravitreal ranibizumab.

**Convenience**
There is no requirement for monitoring between injections of aflibercept in year 1. For ranibizumab, monitoring is suggested following each injection in case of infection.

**Risk assessment**
Not completed.

**Budget impact**

<table>
<thead>
<tr>
<th>Drug costs (per patient) for aflibercept and ranibizumab</th>
<th>Basic NHS Cost per vial</th>
<th>Cost for 1st year</th>
<th>Cost per year after 1st year</th>
<th>Estimated number of injections is based on information from the VISTA and VIVID trials and the NICE TA for ranibizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aflibercept</strong> 2mg vial = £816</td>
<td>8-9 vials = £6528 to £7344</td>
<td>2 vials* = £1,632</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ranibizumab (NICE data)</strong> 2.3mg vial = £742.17</td>
<td>8 vials* = £5937.36</td>
<td>2 vials* = £1,484</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

When the costs of monitoring visits are considered, aflibercept may offer an overall cost benefit assuming that no further monitoring visits are required in addition to treatment visits. In a budget impact model produced by the manufacturer of Eylea, aflibercept reduced costs per patient per year by £1,485 when compared to ranibizumab at NHS list prices whilst generating a higher number of QALYs. The following cost assumptions were made within this model;
- Out-patient cost estimated at £193.76
- Cost of a monitoring visit estimated at £139.22
- Cost of fluorescein angiography estimated at £117.00

**Funding**
CCG funded.

**Suggested place in therapy**
Eylea® will provide another option to existing intravitreal ranibizumab for clinicians treating DMO in patients with baseline CRT >400µm and BCVA of 73 to 24 letters (20/40 to 20/230 vision as Snellen equivalent) irrespective of previous VEGF inhibitors or laser therapy. A NICE technology appraisal for aflibercept in DMO is expected in June 2015 which will better determine its place in therapy and cost effectiveness.

1. **Background and introduction**

Diabetic Macular Oedema (DMO) is a common complication associated with diabetic retinopathy and is the most common cause of visual impairment in patients with Diabetes Mellitus (DM). DMO is instigated by persistent hyperglycaemia and inflammation which weakens, and...
eventually leads to the breakdown of, the blood-retinal barrier. This in turn results in accumulation of fluids and proteins in the intraretinal layers (Macula Oedema) and eventually leads to vascular occlusion, ischaemia and hypoxia of the eye. Approximately 15% of people with diabetic retinopathy suffer from DMO and half of these will develop clinically significant disease. If left untreated, 25-30% of eyes with DMO experience moderate vision loss. DMO impacts visual acuity and presents with blurred vision, metamorphopsia, floaters, changes in contrast sensitivity, photophobia and localised deficits of visual fields. VEGF is a vasoactive cytokine which plays a key role in the proliferation of DMO by increasing vascular permeability and stimulating angiogenesis. (1;2)

The current standard of care for sight threatening DMO is focal laser photocoagulation or grid photocoagulation. Laser photocoagulation, however, has limited efficacy and is not suitable for use in all cases. (1-4) NICE also recommends ranibizumab, an inhibitor of VEGF, which is licensed to treat DMO. (5) Intravitreal steroid implants such as iluvien® (fluocinolone acetonide) and Ozurdex® (dexamethasone) offer a treatment option when anti-VEGF agents are unsuitable. (6) Aflibercept is a recombinant fusion protein which has been suggested to have greater binding affinity to VEGF compared with the other VEGF inhibitors, bevacizumab and ranibizumab. (2,4) Aflibercept is currently licensed for age-related macular degeneration (AMD), macular oedema secondary to central retinal vein occlusion and DMO and was launched in August 2014 for DMO. (3) Aflibercept is intended for the treatment of visual impairment due to DMO and would offer patients an alternative to laser therapy or to ranibizumab. (3)

2. Proposed place in therapy
Ranibizumab is currently the NICE approved VEGF inhibitor for DMO and a nice TA for Aflibercept in DMO is expected in June 2015. Bayer Healthcare propose the following advantages of aflibercept compared with monthly ranibizumab:(5;7;8)

- Reduced pressure on NHS ophthalmology services from fewer monitoring visits in the first year
- Lower costs to the NHS in treating and monitoring patients in their first year of treatment at the range of acquisition costs.

3. Evidence selected for inclusion
Data from the pivotal phase 3, double-blind, randomised studies (VISTA-DME and VIVID-DME) and a phase 2 dose-finding study (DA VINCI) are included in this review. (4; 9)

VISTA-DME (n=466) and VIVID-DME (n=406) were both randomised, double-blind, active controlled multicentre studies of nearly identical design conducted over 52 weeks. They compared the efficacy and safety of aflibercept with laser photocoagulation therapy in patients with DMO. Patients were included if they had type 1 or 2 DM (most patients included had type 2 DM), presented with central DMO with central retinal thickening (CRT) at baseline ranging from 479 micrometres (µm) to 483µm in VISTA-DME and from 502µm to 540µm in VIVID-DME, in addition to best correct visual acuity (BCVA) of 73 to 24 letters (20/40 to 20/230 vision as Snellen equivalent) at baseline. VISTA-DME was carried out at over 54 sites in the USA and VIVID-DME was carried out over 73 sites across Europe, Japan and Australia. Follow up to 148 weeks is on-going for both.

In both VISTA-DME and VIVID-DME studies, patients were randomised 1:1:1 to one of three groups; intravitreal aflibercept 2mg monthly (2q4), 2mg every 8 weeks after 5 initial monthly doses (2q8) or macular laser photocoagulation.

The primary efficacy endpoint (mean change in BCVA from baseline) was superior in both 2q4 and 2q8 groups compared with the laser group in both studies. In VISTA-DME, there were gains of +12.5 [+/- 9.5] letters and +10.7 [ +/- 8.2] letters in the 2q4 and 2q8 aflibercept groups respectively compared with +0.2 (+/- 12.5) letters in the laser photocoagulation group (p<0.0001). In VIVID-DME, there were gains of +10.5 [+/- 9.5] letters and +10.7 [ +/- 9.3] in the 2q4 and 2q8 aflibercept groups respectively compared with +1.2 [+/- 10.6] letters in the laser photocoagulation group (p<0.0001). In the 2q4 group of VISTA-DME and of VIVID-DME, 11.8 and 12.2 aflibercept injections were administered over 52 weeks and in the 2q8 group, 8.4 and 8.7 injections were administered in both studies respectively. At week 52, significant superiority was demonstrated for the 2q4 and 2q8 regimens of aflibercept over laser photocoagulation in both significant visual acuity gains and prevention of severe loss of visual acuity. In terms of secondary endpoints from baseline to 52 weeks, significantly more eyes treated with aflibercept compared to laser photocoagulation gained >10 and >15 letters in BCVA and greater improvements in Diabetic Retinopathy Severity (DRSS) scores and in CRT were observed. The change from baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ1) was similar across all groups in VIVID-DME and different from laser only for the aflibercept 2q4 group in VISTA-DME. (4)

The DA VINCI study was a phase 2, randomised, double-blinded, active controlled multicentre study which evaluated aflibercept vs. laser photocoagulation therapy in patients with DMO over 52 weeks. Adults (n=221) with type 1 or 2 DM with clinically significant diabetic macular edema (DME) were randomised to receive aflibercept 2mg every 4 weeks (0.5mg every 8 weeks (0.5q4, n=44), 2mg every 4 weeks (2q4, n=44), 2mg for three initial monthly doses then every 8 weeks (2q8, n=42) or 2mg for three initial monthly doses then as required, (2qPRN, n=45). The active control group received laser photocoagulation at baseline and then as needed (but no more frequently than every 16 weeks (q16, n=44), which was longer than the interval used in current practice. Patients were excluded from the study if they had received treatment within 3 months of screening or if they suffered with any other ocular or systemic disorders that could contribute to vision loss. To maintain blinding, eyes in the laser group also received a sham injection every 4 weeks and eyes in the aflibercept groups received sham laser treatment. After 24 weeks, laser treatment was provided as ‘rescue’ therapy in VEGF groups if pre-defined criteria indicating treatment failure were met. Over 52 weeks, aflibercept injections were administered the following number of times; 0.5q4 (11.7 injections), 2q4 (10.8 injections), 2q8 (7.2 injections), 2qPRN after loading (7.4 injections) and 2.5 sessions of laser photocoagulation were required. The primary outcome analysis was the change in BCVA from baseline to week 24. Patients in the aflibercept groups gained between +8.5 to +11.4 letters compared with a loss of +2.5 letters in the laser photocoagulation group (p<0.001, for each dosing regimen of aflibercept). Further analyses showed these results were maintained through to week 52. (8; 9)

4. Critical evaluation

4.1. Clinical application
Although VIVID-DME and VISTA-DME were of similar design, there were important differences in their populations; more patients in VISTA-DME had received prior anti-VEGF therapy before enrolment compared to VIVID-DME (42.9% vs. 8.5%) so patients in VISTA-DME probably had DMO of a

more refractory nature. In terms of limitations, it was not well understood how well the visual acuity outcomes measured in the VIVID™ and VISTA™ DME correlate with patient’s quality of life (QoL); in both studies, the worse seeing eye was treated, whereas the QoL score was based on overall visual function. Detail on randomisation and allocation concealment was limited and the initial study protocol was amended due to fluctuation seen in CRT, so that patients were loaded with 5 initial doses rather than the 3 originally intended. Finally, though the design was double-blinded, treatment involved an unmasked physician who was not involved in analysis, which may have led to bias, though there was no evidence of this. Exclusion criteria were not described in the study manuscripts so extrinsic validity was difficult to assess. (4) The DA VINCI study was not adequately powered to detect differences between the various dosing regimens of aflibercept. A significant limitation of the DA VINCI study was that giving laser treatment up to every 16 weeks (rather than up to every 12 weeks) may have led to an overestimation of the comparative efficacy of aflibercept. With respect to other limitations, the protocol stated that one eye was treated per patient but was not clear on how this eye was selected and how this impacted on quality of life. (10)

Overall, data from the two large VIVID and VISTA studies of aflibercept in DMO demonstrated that the licensed dosing regimen of 2mg per month for five consecutive doses, followed by 2mg every two months for up to a year was superior to laser photocoagulation given up to every three months. Efficacy beyond two years will be established with longer term studies which are still on-going. (4) Although there are no studies comparing aflibercept and ranibizumab directly in DMO, there is an independent comparison study in progress (11) and indirect comparisons (1;2); these are described below which generally support that aflibercept and ranibizumab have at least similar efficacy.

- A phase 3 prospective randomised, single blinded parallel group study (NCT01627249, n=660) sponsored independently by the US National Institute of Health is in progress and plans to provide direct comparison data for intravitreal monthly aflibercept (2mg), bevacizumab (1.25mg) or ranibizumab (0.3mg) up to every 4 weeks in patients DMO using defined retreatment criteria. Estimates of treatment effect were based on the mean change in BCVA at a common follow up time point and the percentage of patients with >10 letter gain. From a preliminary analysis, the mean visual-acute letter score (range, 0 to 100, with higher scores indicating better visual acuity and a score of 85 representing approximately 20/20 vision) improved by 13.3 with aflibercept, by 9.7 with bevacizumab, and by 11.2 with ranibizumab. The small difference was not considered clinically meaningful, because it was driven by the eyes with worse visual acuity at baseline with one fewer injection of aflibercept needed over 52 weeks and fewer rescue treatments. A full set of data will become available once the study has been completed, which is expected in the final quarter of 2015. (11;12)

- An indirect comparison study of intravitreal aflibercept, pegaptanib, bevacizumab or ranibizumab was carried out using data from the relevant published literature. Data were included in the meta-analysis if the following study criteria were met: controlled with laser photocoagulation or sham injection with rescue laser therapy available, were of at least fair quality, had 6-24 months of follow up and included measures of change in visual acuity including BCVA, LogMAR or ETDRS. Fifteen RCT’s and 8 observational studies were included and 11 were considered to be of fair to good quality. The magnitude of improvement in visual acuity was similar across the anti-VEGF agents with no statistically significant differences in BCVA or in gains of >10 letters between the between the agents. Most improvements were in the 6-9 letter range for all agents except for pegaptanib for which improvements were in the 4-5 letter range. The obvious limitation of this is that it was an indirect comparison of heterogeneous data and some studies were single-blinded and of poorer quality such as those involving unlicensed bevacizumab. (1)

- Another indirect comparison study was a Cochrane Review which included studies in the analyses dataset if they met certain quality criteria. Data on aflibercept came from DA VINCI, VISTA™ DME and VIVID™ DME studies which were compared with data for other VEGF inhibitors in DMO studies such as RISE-RIDE, RESOLVE and RESTORE. Authors concluded that there were no discernable differences between aflibercept, bevacizumab and ranibizumab with respect to their efficacy. The absolute NNT was 6 (i.e. 5 people had to be treated (95% CI; 3 to 8) with a VEGF inhibitor vs. laser photocoagulation to allow one person to markedly improve their vision. (2)

Afibercept offers an alternative treatment option in the UK to the existing NICE approved treatment ranibizumab. The NICE approved criteria for the use of ranibizumab, based on the relevant published literature includes study inclusion criteria, is for patients with DMO whose eye has a CRT of 400µm or more at the start of treatment. (5) The pivotal aflibercept trials included a similar set of patients with central DMO (CRT at baseline ranged from 479µm to 483µm in VISTA™ DME and from 502µm to 540µm in VIVID™ DME) and BCVA of 73 to 24 letters (20/40 to 20/230 vision as Snellen equivalent) at baseline. (4) Patients included in the pivotal VISTA™ DME and VIVID™ DME studies had received prior anti-VEGF therapy for DMO, though VISTA™ DME included a far greater proportion at baseline compared with VIVID™ DME (average 42.9% vs 8.9%, respectively). Despite the differences with respect to prior anti VEGF use for DMO at baseline, BCVA gains with aflibercept regimens were similar across both studies in the subgroups of eyes with and without prior anti-VEGF therapy. (4) Hence patients with DMO who have been tried on another VEGF inhibitor such as ranibizumab may benefit from aflibercept as well as those who are treatment naive. The RISE and RIDE studies of ranibizumab also included patients who had received previous treatment for DMO and also suggested benefits of ranibizumab regardless of history of prior DME therapy. (13)

4.2 Safety

4.2.1. Key adverse events

In VISTA™ DME, VIVID™ DME and DA VINCI there were no clinically relevant differences between groups in incidence or in the pattern of adverse events or effects (P=0.40), hospitalisation (P=0.51), death (P=0.72), or major cardiovascular events (P=0.56). (12)

4.3 Potential advantages and disadvantages over existing technologies

4.3.1 Convenience

Given that aflibercept was superior to laser photocoagulation, (4;10) the most relevant compactor is ranibizumab which, like aflibercept, is administered in an outpatient or day case ophthalmology setting. Key drivers for cost-effectiveness are the number of injections required over several years and the number of visits required for monitoring. Treatment with aflibercept is proposed to require patients to attend four fewer ophthalmology visits for monitoring in the first year compared with ranibizumab. (8)

Number of treatment visits: The number of treatment visits would be the same throughout the course of several years for both aflibercept and ranibizumab according to their licenses and economic modelling data from Bayer Healthcare. The economic model suggests that 7.9
treatment visits for ranibizumab would be required in year 1. The clinical specialists involved in producing the NICE TA, however, anticipated that people with DMO would need between 7 and 9 treatments in the first year. (5) The aflibercept patients in VISTA	extsuperscript{DME} and VIVID	extsuperscript{DME} who were on the licensed regimen (2q8), received 8.4 and 8.7 injections, respectively, so the number of treatment visits would be between 8 and 9. After 1 year, as the model reasonably assumes in the absence of long term data for aflibercept, the frequency of injections for aflibercept would be equal to that of ranibizumab. This is based on data from the pivotal studies and a survey of 30 UK based ophthalmologists conducted by Bayer Healthcare. Individual localities should check their local ranibizumab usage for more accurate comparative data. (8)

Number of monitoring visits: The license for aflibercept in DMO states that there is no requirement for monitoring between injections in the first year (3) For ranibizumab, the manufacturers recommend monthly monitoring following each injection in case of infection but in practice there is suggestion that monitoring intervals may be extended to 6 weeks after the initial loading phase of ranibizumab. (14;15) Again, individual localities should check the average frequency of actual monitoring visits for patients with DMO who are being treated with ranibizumab for more accurate comparative data. (8;15)

Estimated number of treatments and monitoring visits per year in the model provided by Bayer Healthcare

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Treatment visits</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept</td>
<td></td>
<td>8.0</td>
<td>4.0</td>
<td>2.3</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td></td>
<td>7.9</td>
<td>4.0</td>
<td>2.3</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Laser</td>
<td></td>
<td>2.4</td>
<td>1.0</td>
<td>0.8</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>Monitoring visits</td>
<td>8.0</td>
<td>6.3</td>
<td>4.0</td>
<td>4.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td></td>
<td>12.0</td>
<td>6.3</td>
<td>4.0</td>
<td>4.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Laser</td>
<td></td>
<td>4.0</td>
<td>4.0</td>
<td>2.6</td>
<td>2.2</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Practical Considerations

- Aflibercept and ranibizumab require refrigerated storage and may then be kept at room temperature 24 hours before use. (3;14)
- Aflibercept, like ranibizumab needs to be given by qualified and trained physicians using aseptic technique. (3;14)
- There is an inherent risk of overdose with both aflibercept and ranibizumab since the injections vials contain some excess which must be discarded prior to injection. (3;14)
- Some expertise is required in manipulating injection vials of aflibercept and of ranibizumab; a filter needle is used to withdraw the solution from the vial and then the needle is changed prior to intravitreal injection. Ranibizumab, however, is available as a pre-filled syringe which avoids the use of a filter needle. (3;14)
- A local risk assessment is advised prior to use of any of the anti VEGF agents.

4.3.2 Healthcare resource utilisation

Both aflibercept and ranibizumab are available with confidential simple patient access schemes in England and Wales; as such budget holders are advised to contact a procurement specialist for advice. Acquisition costs are £816 and £742.17 per unit for aflibercept and ranibizumab respectively. Reduced pressure on NHS ophthalmology services, from four fewer monitoring visits, is proposed for aflibercept over ranibizumab. Beyond the first year additional monitoring (supplementary to treatment visits) may be required to the schedule of VEGF injections so any benefit with regards to resource utilisation is likely in the first year only. (8) Even in the first year for aflibercept, there might be additional local appointments (e.g. for monitoring to assess progression of disease in each eye), which may negate this potential benefit.

4.3.3 Suitability for shared care

Not suitable for Shared Care as aflibercept has to be administered by a trained specialist.

4.3.4 Drug cost and likely budgetary impact

The costs associated with DMO treatment and subsequent monitoring are high. The following table considers only drug costs, which may be required to the schedule of aflibercept and ranibizumab. With regards to the frequency of injections, individual localities should check their local ranibizumab usage to allow a more accurate comparison.

Table 1: Drug costs (per patient) for aflibercept and ranibizumab

<table>
<thead>
<tr>
<th></th>
<th>Basic NHS Cost per vial</th>
<th>Cost for 1st year</th>
<th>Cost per year after 1st year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept 2mg vial</td>
<td>£816</td>
<td>8-9 vials* = £6,528 to £7,344</td>
<td>2 vials* = £1,632</td>
</tr>
<tr>
<td>Ranibizumab (NICE data)</td>
<td>£742.17</td>
<td>8 vials* = £5,937.36</td>
<td>2 vials* = £1,484</td>
</tr>
</tbody>
</table>

* Frequency of injections are based on information from the VISTA and VIVID trials/manufacturer data for aflibercept (4); NICE TA for ranibizumab and represents the mean average of treatments used annually in years 2-4. (5)

(see further discussion under section 4.3.1 convenience)

5 Health Economics

The economic model developed by Bayer Healthcare (8) estimated the lifetime clinical and economic outcomes of different treatments for the management of patients with DMO with a baseline BCVA of ≤75 letters, which reflected the population included in the VISTA	extsuperscript{DME} VIVID	extsuperscript{DME} trials. The model considered aflibercept 2 mg administered in a fixed-dose regimen that may be extended after the first year, with no requirement for monthly monitoring between injections, and was compared to ranibizumab and laser photocoagulation. Incremental cost effectiveness ratios (ICER) were calculated as the incremental cost per Quality Adjusted Life Year (QALY) gained for aflibercept vs. ranibizumab and laser. The willingness-to-pay (WTP) threshold used in the analysis was set to £30,000 per QALY gained. One-way sensitivity analysis (OWSA) and probabilistic sensitivity analyses (PSA) were performed on all key variables. In the base case analyses, aflibercept reduced costs per patient per year by £1,485 when compared to ranibizumab at NHS list prices whilst generating a higher number of QALYs.
Intravitreal aflibercept will provide another option to existing intravitreal ranibizumab for clinicians treating DMO in patients. Aflibercept, like ranibizumab, has a dosing frequency of one injection every 8 weeks. The cost per unit of aflibercept and ranibizumab respectively £816 and £742.17. The cost of a treatment visit (out-patient cost) is estimated at £193.76.

The OWSA indicated that results in both comparisons were most sensitive to shorter time horizons and to the cost of aflibercept when compared to laser. Probabilistic analysis showed that the probability that aflibercept is cost-effective when compared to ranibizumab and laser is 0.937 and 0.837 respectively at a WTP of £30,000. A sub-group analysis conducted in patients with a baseline CRT >400 found aflibercept to be dominant compared to ranibizumab and laser, generating an ICER per QALY of £15,261. The main strength of the model is the inclusion of outcomes based on both eyes, considering all the possible permutations of BCVA in both the better and worse seeing eyes. The main weakness of this study is the lack of comparative data beyond two years meaning that assumptions were required to model the impact of treatment on BCVA beyond this point. Two key assumptions were that vision among treated patients is assumed to remain stable for 4 years during the maintenance phase and in years 2 to 5, in the absence of other evidence, treatment and monitoring frequency is assumed to be the same for aflibercept as for ranibizumab.

### 6 Likely commissioning and funding pathway

Aflibercept, like ranibizumab, is expected to be funded and commissioned by Clinical Commissioning Groups.

### 7 Suggested place in therapy

Intravitreal aflibercept will provide another option to existing intravitreal ranibizumab for clinicians treating DMO in patients with baseline CRT ≥400μ and BCVA of 73 to 24 letters (20/40 to 20/230 vision as Snellen equivalent) irrespective of previous VEGF or laser therapy for DMO. A NICE technology appraisal for aflibercept in DMO is expected in June 2015 which will better determine its place in therapy and cost effectiveness. 

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**Table 2: Base case results**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Costs (£)</th>
<th>QALYs gained</th>
<th>Incremental costs (£)</th>
<th>Incremental QALYs</th>
<th>ICER/QAL(£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept</td>
<td>38,071</td>
<td>7,690</td>
<td>-1,485</td>
<td>0.092</td>
<td>Dominant</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>39,556</td>
<td>7,598</td>
<td>0.340</td>
<td>3,498</td>
<td>12,792</td>
</tr>
<tr>
<td>Laser</td>
<td>33,083</td>
<td>7,300</td>
<td>1,485</td>
<td>0.340</td>
<td>12,792</td>
</tr>
</tbody>
</table>

Assumptions;
- The cost of a treatment visit (out-patient cost) is estimated at £193.76.
- The cost of a monitoring visit = £139.22, and fluorescein angiography is estimated at £117.00.
- The cost per unit of aflibercept and ranibizumab respectively £816 and £742.17.
- Both aflibercept and ranibizumab are available with confidential simple patient access schemes in England and Wales. (5;5;8)(5;8)

The OWSA indicated that results in both comparisons were most sensitive to shorter time horizons and to the cost of aflibercept when compared to laser. Probabilistic analysis showed that the probability that aflibercept is cost-effective when compared to ranibizumab and laser is 0.937 and 0.837 respectively at a WTP of £30,000. A sub-group analysis conducted in patients with a baseline CRT ≥400 found aflibercept to be dominant compared to ranibizumab and laser, generating an ICER per QALY of £15,261. The main strength of the model is the inclusion of outcomes based on both eyes, considering all the possible permutations of BCVA in both the better and worse seeing eyes. The main weakness of this study is the lack of comparative data beyond two years meaning that assumptions were required to model the impact of treatment on BCVA beyond this point. Two key assumptions were that vision among treated patients is assumed to remain stable for 4 years during the maintenance phase and in years 2 to 5, in the absence of other evidence, treatment and monitoring frequency is assumed to be the same for aflibercept as for ranibizumab.

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**Reference List**

7. Summary of Product Characteristics. Eylea 40mg/ml solution for injection (vial), Date of revision of the text: 08/2014 Bayer Healthcare Ltd. www.medicines.org.uk
15. Personal communication. Novartis Pharmaceuticals