

[aflibercept 40mg/mL solution for injection \(Eylea®\)](#)

SMC No. (1074/15)

Bayer

07 August 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

aflibercept (Eylea®) is accepted for use within NHS Scotland.

Indication under review: for adults for the treatment of visual impairment due to macular oedema secondary to branch retinal vein occlusion.

Aflibercept was associated with significant improvements over laser in visual acuity during a 6-month, randomized, double-masked phase III study in patients with branch retinal vein occlusion.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of aflibercept. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

Aflibercept has previously been accepted by SMC for macular oedema secondary to central retinal vein occlusion. This advice now extends its use to patients with macular oedema secondary to branch retinal vein occlusion.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

For adults for the treatment of visual impairment due to macular oedema secondary to branch retinal vein occlusion.

Dosing Information

By intravitreal injection, 2mg aflibercept every month. The interval between two doses should not be shorter than one month. If visual and anatomic outcomes indicate that the patient is not benefitting from continued treatment, aflibercept should be discontinued. Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a treat and extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography).¹

Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections.

Product availability date

25 February 2015

Summary of evidence on comparative efficacy

There are two types of retinal vein occlusion: branch retinal vein occlusion (BRVO) which is due to blockage of one of the four retinal veins, each of which drains about a quarter of the retina, and central retinal vein occlusion (CRVO) which is due to blockage of the main retinal vein, which drains blood from the whole retina. Loss of visual acuity is usually secondary to macular oedema which results from leakage of fluid from the capillaries and is generally more severe if the central retinal vein is blocked. However, the incidence of BRVO is two to three times higher than CRVO.¹

Aflibercept is a human recombinant fusion protein that inhibits the binding of vascular endothelial growth factor A (VEGF-A) to its receptors, thereby preventing endothelial cell proliferation, neovascularisation and vascular leakage, which are all thought to be contributing factors in the progression of visual impairment caused by macular oedema. Aflibercept is also licensed for the treatment of adults with visual impairment due to macular oedema secondary to CRVO, due to diabetic macular oedema macular and for neovascular (wet) age-related macular degeneration (AMD).² It has been accepted for use in CRVO and AMD and for restricted use for diabetic macular oedema in NHS Scotland by the Scottish Medicines Consortium.

The evidence to support the use of aflibercept in patients with BRVO comes from one randomised, double-masked, phase III study (VIBRANT).^{3,4} Eligible patients were aged at least 18 years and had BRVO or hemi retinal vein occlusion (HRVO) diagnosed within 12 months, causing oedema with Best Corrected Visual Acuity (BCVA) of ≤ 73 and ≥ 24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent 20/40 to 20/320). Only one eye from each patient was treated in the study. BRVO was defined as the presence of retinal haemorrhages or other bio-microscopic evidence of RVO and a dilated venous system in less than two quadrants of the retina drained by the same vein.

HRVO was defined as an RVO that involved two retinal quadrants. A total of 183 patients were randomised equally to receive aflibercept (2mg intravitreally every 4 weeks from baseline to week 20 then 2mg intravitreally every 8 weeks to week 52 plus sham grid laser photocoagulation on day 1) or grid laser photocoagulation (on day 1 plus sham aflibercept intravitreally every 4 weeks from baseline to week 20 then every 8 week to week 52). Randomisation was stratified by region (Japan and North America) and baseline BCVA letter score (35 to 73 and 24 to 34).

Rescue treatment with active laser treatment was allowed in the aflibercept group at week 36 or at week 12, 16, 20, in the laser group (provided 12 weeks had passed since last active treatment). Patients in the laser group could also receive rescue aflibercept treatment from week 24 (three doses of 2mg intravitreally every 4 weeks, then 2mg intravitreally every 8 weeks). At least one of the following criterion was to be met to be eligible for rescue treatment:

- >50 micrometre increase in central retinal thickness (CRT) compared with lowest previous measurement
- Presence of new or persistent cystic retinal changes, sub-retinal fluid or persistent diffuse oedema in central optical coherence tomography subfield
- Loss of ≥ 5 letters compared with best previous measurement due to BRVO plus any increase in CRT

The primary outcome was the proportion of eyes that gained ≥ 15 ETDRS letters in BCVA from baseline to week 24. This was achieved by significantly more patients in the aflibercept than in the laser group. The treatment effect was generally consistent across subgroups. The table below details results of the primary and secondary outcomes.

Table: Results of primary and key secondary outcomes in the VIBRANT study^{3,4}

	Aflibercept (n=91)	Laser (n=90)	Difference (95% CI), p-value
Primary Outcome			
Proportion with a gain of ≥ 15 ETDRS letters in BCVA from baseline to week 24.	53% (48/91)	27% (24/90)	27% (13% to 40%) p=0.0003
Secondary Outcomes			
Mean change (\pm SD) from baseline to week 24 in BCVA score	17.0 (± 11.9)	6.9 (± 12.9)	10.5* (7.1 to 14.0) p<0.0001
Mean change (\pm SD) from baseline in CRT at week 24 (micrometres)	-280.5 (± 189.7)	-128.0 (± 195.0)	-148.6* (-179.8 to -117.4) p<0.0001

* Least square mean difference; CI=confidence interval; ETDRS= Early Treatment Diabetic Retinopathy Study; BCVA=best corrected visual acuity; SD=standard deviation; CRT=central retinal thickness

Quality of life was measured using the National Eye Institute visual functioning questionnaire-25 (NEI VFQ-25), which ranges from 0 (worse possible state) to 100 (best possible state). At week 24, there was no significant difference in mean (\pm SD) change from baseline in NEI VFQ-25 total score in the aflibercept and laser groups: 7.7 (± 11.08) versus 6.3 (± 12.34) respectively.²

At week 52, the primary and secondary outcomes also significantly favoured aflibercept over laser. Significantly more aflibercept than laser patients gained ≥ 15 ETDRS letters in BCVA (57% [52/91] versus 41% [37/90] respectively, p=0.0296) and there were significantly greater changes from baseline in BCVA score (17.1 [± 13.1] versus 12.2 [± 11.9] respectively, p<0.0035) and in CRT (-283.9 micrometres versus -249.3 micrometres, respectively, p=0.022). By week 52, rescue treatment had been administered in 9.9% of aflibercept and 74% of laser patients.

Summary of evidence on comparative safety

Safety data up to week 24 are more pertinent than later data as after this point rescue treatments were permitted; by week 52, 74% of laser patients received rescue aflibercept (mean of 4.4 injections) and 10% of aflibercept patients received rescue laser treatment.⁴

At week 24, adverse events were reported in 64% (58/91) of aflibercept patients and 59% (54/92) of laser patients. These included ocular adverse events in 37% and 27% respectively and non-ocular adverse events in 47% and 50% respectively. At week 24, the following ocular adverse events had been reported in the aflibercept and laser groups respectively: conjunctival haemorrhage (20% versus 4.3%); eye pain (4.4% versus 5.4%); eye irritation (4.4% versus 1.1%); foreign body sensation in the eye (3.3% versus 0%); increased lacrimation (3.3% versus 0%); corneal epithelium defect (2.2% versus 0%); vitreous detachment (2.2% versus 0%); cataract (2.2% versus 0%); increased ocular pressure (2.2% versus 0%); retinal neovascularisation (0% versus 3.3%); dry eye (1.1% versus 2.2%); macular fibrosis (1.1% versus 2.2%); macular oedema (1.1% versus 2.2%).⁴

At week 24, the following non-ocular adverse events had been reported in the aflibercept and laser groups: hypertension (6.6% versus 11%); nasopharyngitis (6.6% versus 5.4%); bronchitis (4.4% versus 1.1%); upper respiratory tract infection (4.4% versus 0%); increased blood pressure (3.3% versus 4.3%); headache (0% versus 3.3%); influenza (3.3% versus 1.1%).⁴

Summary of clinical effectiveness issues

BRVO is an important cause of vision loss, particularly in patients with associated chronic macular oedema. Current treatment options for patients with macular oedema secondary to BRVO are intravitreal ranibizumab which, like aflibercept, is administered monthly, or intravitreal dexamethasone which is administered as a single implant, although retreatment is allowed if required. Ranibizumab has been accepted by SMC for use in NHS Scotland for adults for the treatment of visual impairment due to macular oedema secondary to BRVO and dexamethasone accepted for restricted use in patients with BRVO who are not clinically suitable for laser treatment including patients with dense macular haemorrhage or patients who have received and failed on previous laser treatment.

The evidence is limited to one pivotal study, in 181 patients, which demonstrated statistically and clinically significant improvements in visual acuity for aflibercept compared with laser in the indication under review. This was supported by secondary outcomes including change in CRT. There was a numerical but not statistically significant improvement in quality of life between groups assessed by the NEI VFQ-25 total score. This may have been due to good vision in the other eye and only modest visual impairment in some study eyes.³

In the study, aflibercept was administered every four weeks from baseline to week 20.³ This may differ from aflibercept dosing in clinical practice as recommended by the summary of product characteristics (SPC) which states that monthly treatment should continue until maximum visual acuity is achieved and/or there are no signs of disease activity.² The study excluded patients with diabetic retinopathy which may also be present in patients with RVO in clinical practice.³

The study compared aflibercept with laser treatment which was a relevant comparator for the treatment of BRVO when the study was designed. However, other agents have since been licensed for the treatment of BRVO and there are no direct comparative data with these. Therefore, the submitting company presented a network meta-analysis (NMA), using Bayesian methods, to compare

the efficacy of aflibercept and ranibizumab in patients with BRVO. The NMA included four studies in the base case and an additional four studies in a sensitivity analysis. Two outcomes assessed at 24 weeks were included: proportion of patients gaining ≥ 15 letters from baseline and the change in BCVA from baseline. The NMA suggested that aflibercept was similar to ranibizumab in both outcomes. A limitation of the NMA was heterogeneity due to some differences between two of the studies included in the base case in terms of prior treatment and rescue treatment. Limited available data for the two other studies in the base case meant that it was not possible to compare the characteristics of the study populations. Probabilities were not reported to support the NMA results. There was no comparison of safety outcomes. A recently published NMA has also suggested that aflibercept and ranibizumab have similar efficacy in the treatment of macular oedema secondary to BRVO.⁵ The submitting company did not provide any indirect comparative data with dexamethasone.

Service implications concerning aseptic administration and frequency of injections of aflibercept are similar to those required for ranibizumab. The SPC for aflibercept recommends that monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a treat and extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes; however, there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response.² While reduced frequency of monitoring may be an advantage for the service in terms of cost and capacity savings, there is no evidence at present that the use of aflibercept would result in reduced frequency of injections or monitoring compared with ranibizumab.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing aflibercept with ranibizumab in patients with visual impairment due to macular oedema secondary to BRVO. The company provided market research data to show ranibizumab is the main treatment used for BRVO and SMC clinical experts have confirmed that the comparator is appropriate.

A lifetime Markov model was used where health states were defined by different stages of visual acuity. The model consisted of three separate phases: the efficacy phase which lasts 6 months, the maintenance phase up to year 5, and the 'rest of life' phase beyond year 5. The efficacy phase is the only period of the model in which patients may experience an improvement in vision. In the maintenance phase, stable vision is assumed based on patients continuing to receive treatment in order to stabilise vision. Finally, the 'rest of life' phase captures the long-term decline in visual acuity over time after treatment has stopped.

The clinical data from the VIBRANT study were used to estimate transition probabilities for the aflibercept arm of the model. For the ranibizumab arm, the transition probabilities were estimated based on the odds ratios versus aflibercept from the NMA. The NMA showed that aflibercept and ranibizumab have comparable efficacy, but the numerical differences in efficacy from the NMA were used in the model. After the efficacy phase of the model, the benefit obtained from treatment was assumed to be maintained until year 5. Beyond year 5, patients stopped treatment and visual acuity was assumed to decline in line with natural disease progression.

The utility values used in the model were taken from a published study in which the time trade-off method was used to obtain utility values associated with age-related macular degeneration health states from members of the UK population. The company noted that while this study was not specific

to visual acuity in patients with macular oedema secondary to BRVO, the results have been accepted previously as being generalisable to other eye conditions.

The analysis included the drug acquisition and administration costs of aflibercept and ranibizumab. A patient access scheme (PAS) is in place for ranibizumab and the analysis included an estimate of the PAS price of ranibizumab. Treatment frequency and resource use were assumed to be equal in each arm of the model. In the first 6 months, the number of injections in each arm was 5.7 based on the mean number of injections administered in the aflibercept and ranibizumab studies (VIBRANT and BRAVO). For months 7-12 in the model, the company again assumed the same number of injections in each arm based on the ranibizumab study (2.7) although the number of injections in the aflibercept study was higher (3.3). The number of injections in each arm in years 2 to 5 was 4.15, 2.61, 1.12 and 0.58 respectively, based on clinical opinion. Other resource use included monitoring visits, which included an eye test and an optical coherence tomography test. The cost of fluorescein angiography, costs associated with adverse events (cataract and ocular hypertension), and cost of blindness were also included.

A PAS was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price. In the base case analysis with the aflibercept PAS and including an estimate of the ranibizumab PAS, the company estimated that aflibercept was the dominant treatment. A range of sensitivity analyses were presented which showed the key driver of the model was the relative efficacy of aflibercept and ranibizumab based on the odds ratio from the NMA. It is SMC policy to include the estimated quality-adjusted life-year (QALY) gain in the detailed advice document for all submissions. However, owing to commercial in confidence concerns regarding the PAS, SMC is unable to publish this figure.

The following limitations were noted:

- The more relevant analysis is a scenario analysis which showed that aflibercept remained cost-saving compared to ranibizumab with the PAS. Aflibercept also remained cost-saving when a one-year time horizon was used.
- The analysis assumed the number of injections administered is the same in both arms. Data from the relevant aflibercept (VIBRANT) and ranibizumab (BRAVO) studies showed the mean number of injections in year 1 was slightly higher in the aflibercept study (9 vs 8.4). To explore this further, the company provided sensitivity analysis using the number of injections administered in the studies. This resulted in an incremental cost with aflibercept. However, the company noted the difference in the number of injections is due to a difference in the study protocols rather than a difference in how the treatments would be administered in practice.

Despite the limitations, the economic case has been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified patient groups.

- A joint submission was received from the Royal National Institute of Blind People (RNIB) and The Macular Society, which are both registered charities.
- The RNIB has received pharmaceutical company funding in the past two years, including from the submitting company. The Macular Society has not received any pharmaceutical company funding in the past two years.
- Macular oedema (MO) secondary to branch retinal vein occlusion (BRVO) damages central vision and therefore has a substantial negative impact on daily living activities and quality of life. Changes in vision are sudden and if left untreated or if a patient does not respond to or is unsuitable for current treatments, they are at risk of: loss of independent living, loss of employment, increased anxiety and stress associated with sudden vision loss and fear of going blind. Patients can depend very much on family and carers for practical and emotional support.
- Not all patients respond to, or can tolerate the currently available therapies in NHS Scotland. In addition, some patients reported that there was a noticeable improvement in their vision if they switched between treatments.
- Aflibercept would provide patients with another treatment option with evidence of efficacy and tolerability that could mean the difference between losing sight and saving existing sight. It could enable patients to better manage their condition better and carry out daily living activities, improving their well-being and that of their carers.

Additional information: guidelines and protocols

The Royal College of Ophthalmologists published Interim Guidelines for the Management of Retinal Vein Occlusion in December 2010.¹ These guidelines provide separate recommendations for CRVO and BRVO. In BRVO with no or minimal evidence of macular ischaemia, there are recommendations for dexamethasone and ranibizumab when seen within three months of onset and for laser, dexamethasone and ranibizumab when seen after three months of onset. It is noted that laser photocoagulation is beneficial only after three to six months, after absorption of the majority of haemorrhage. However patients with severe vision loss and with symptoms persisting for more than one year are unlikely to benefit. In BRVO with evidence of marked macular ischaemia, no immediate treatment is recommended but to watch for conversion to ischaemic type and subsequent neovascularisation.

These guidelines predate the licensing of aflibercept for macular oedema following BRVO.

Additional information: comparators

The relevant comparators are ranibizumab, dexamethasone implants and laser photocoagulation.

Cost of relevant comparators

Drug	Dose Regimen	Cost per 6 months (£)
Aflibercept	2mg by intravitreal injection every month until visual acuity is achieved	Up to 4,896
Ranibizumab	0.5mg by intravitreal injection every month until visual acuity is achieved	Up to 4,452
Dexamethasone	700 micrograms by single intravitreal implant	870

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eMIMS on 20 May 2015 and based on treatment of one affected eye per patient. The cost of dexamethasone is based on one implant. Costs of aflibercept and ranibizumab based on up to six doses. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 994 patients eligible for treatment in year 1 rising to 5,008 in year 5 with an assumed uptake rate of 50% in each year and a small proportion of discontinuations.

Without PAS:

The company estimated a gross medicines budget impact of £3.4m in year 1 and £6.9m in year 5. As other medicines were assumed to be displaced, the net budget impact was estimated to be £308k in year 1 and £625k in year 5. Note that these figures are based on the list price for both aflibercept and ranibizumab.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. The Royal College of Ophthalmologists. Interim Guidelines for Management of Retinal Vein Occlusion, December 2010.
2. Bayer plc. Summary of product characteristics, Eylea® 40mg/mL solution for injection in a vial. Last updated 19 March 2015
3. Campochiaro PA, Clark WL, Boyer DS et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion. The 24-week results of the VIBRANT study. *American Academy of Ophthalmology* 2015;122:538-44.
4. The European Medicines Agency (EMA) European Public Assessment Report. Aflibercept (Eylea®), EMA/CHMP/13670/2015, 22 January 2015. www.ema.europa.eu
5. Regnier SA, Larsen M, Bezlyak V, et al. Comparative efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion: a network meta-analysis. *BMJ Open* 2015;5:e007527. doi:10.1136/bmjopen-2014-007527

This assessment is based on data submitted by the applicant company up to and including 16 July 2015.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.