Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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aflibercept, 40mg/mL solution for injection (Eylea®) SMC No. (1003/14)

Bayer

10 October 2014

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

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

Indication under review: For adults for the treatment of visual impairment due to diabetic macular oedema (DMO).

SMC restriction: treatment of visual impairment due to DMO in adults with best corrected visual acuity (BCVA) 75 Early Treatment Diabetic Retinopathy Study (ETDRS) letters or less at baseline.

Intravitreal aflibercept significantly improved BCVA at 52 weeks compared with laser photocoagulation in two phase III, double-masked studies.

This 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 patient access scheme, or a list price that is equivalent or lower, in NHS Scotland.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 10 November 2014

Indication

For adults for the treatment of visual impairment due to diabetic macular oedema (DMO).

Dosing Information

Diabetic Macular Oedema

The recommended dose is 2mg aflibercept equivalent to 50 microlitres. Treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.

After the first 12 months of treatment, the treatment interval may be extended based on visual and anatomic outcomes. The schedule for monitoring should be determined by the treating physician.

If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, aflibercept should be discontinued.

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

Product availability date

August 2014

Summary of evidence on comparative efficacy

One of the most common complications of diabetes mellitus is diabetic retinal disease. DMO, characterised by increasing vasopermeability and damage to retinal capillaries, can lead to visual impairment in patients with diabetic retinopathy. Aflibercept is a potent specific inhibitor of vascular endothelial growth factor (VEGF) and a fully human fusion protein, consisting of soluble VEGF receptors 1 and 2. When administered directly into the vitreous, it reduces retinal thickness. Aflibercept is also licensed for use in adults with neovascular (wet) age-related macular degeneration and visual impairment due to macular oedema secondary to central retinal vein occlusion and has been accepted for use by SMC for these indications.[1,2]

The submitting company has requested SMC considers aflibercept when positioned for use in the treatment of visual impairment due to DMO in adults with best corrected visual acuity (BCVA) 75 Early Treatment Diabetic Retinopathy Study (ETDRS) letters or less at baseline.

Evidence to support the licence extension comes from two similar double masked, randomised, phase III studies, VISTA and VIVID.[2] Both studies compared the efficacy and safety of intravitreal aflibercept with laser photocoagulation in adults with DMO secondary to diabetes mellitus (type I or II) with central involvement. BCVA was assessed using the ETDRS chart. Only one eye per patient was enrolled in the study, patients had a baseline BCVA ETDRS letters score of 73 to 24 in the study eye. VISTA enrolled 466 patients in the United States and VIVID enrolled 406 patients from Europe, Australia and Japan. Patients were randomised equally to receive:

- Intravitreal aflibercept 2mg every four weeks plus sham laser or
- Intravitreal aflibercept 2mg every four weeks for five doses then 2mg every eight weeks (referred to as eight-weekly dosing schedule) plus sham laser or
- Laser photocoagulation plus sham injection

Patients allocated to laser photocoagulation received treatment at baseline then as required based on pre-specified criteria, but not more often than every 12 weeks. At week 24, all patients were allowed additional rescue treatment if worsening DMO caused them to lose 10 or more letters on two consecutive visits or 15 or more letters at any one visit from the best previous measurement. Patients in the aflibercept groups could receive laser photocoagulation and patients in the laser photocoagulation group could receive aflibercept according to the eight-weekly dosing schedule. Patients who received additional rescue treatment were censored in the final analyses.

The primary outcome was change from baseline of BCVA in ETDRS letter score at 52 weeks. In the VISTA study, patients had a mean baseline BCVA of 59, 59, and 60 ETDRS letters in the aflibercept four-weekly group, aflibercept eight-weekly group and laser photocoagulation group respectively. In the VIVID study, patients had a mean baseline BCVA of 61, 59, and 61 ETDRS letters in the aflibercept four-weekly group, aflibercept eight-weekly group and laser photocoagulation group respectively.

Intravitreal aflibercept 2mg four-weekly and eight-weekly significantly improved BCVA from baseline compared with laser photocoagulation in both studies ($p<0.0001$). In the VISTA study, mean change from baseline (±standard deviation [SD]) in BCVA at 52 weeks was +12.5 (±9.5) ETDRS letters in the aflibercept four-weekly group, +10.7 (±8.2) ETDRS letters in the aflibercept eight-weekly group and +0.2 (±12.5) ETDRS letters in the laser photocoagulation group. In the VIVID study, mean change from baseline (±SD) in BCVA at 52 weeks was +10.5 (±9.5) ETDRS letters in the aflibercept four-weekly group, +10.7 (±9.3) ETDRS letters in the aflibercept eight-weekly group and +1.2 (±10.6) ETDRS letters in the laser photocoagulation group. Table 1 describes the secondary outcomes in the VIVID and VISTA studies comparing the aflibercept eight-weekly group (the licensed dosing schedule) with laser photocoagulation and these secondary outcomes supported the primary outcome.

Table 1: Secondary outcomes, change from baseline to week 52.

	VISTA		VIVID	
	Aflibercept eight-weekly	Laser	Aflibercept eight-weekly	Laser
Proportion of patients who gained ≥10 ETDRS letters*	58%	20%	53%	26%
Proportion of patients who gained ≥15 ETDRS letters*	31%	7.8%	33%	9.1%
Proportion of patients who achieved a ≥2-step improvement on the ETDRS diabetic retinopathy (DR) severity scale**	29%	14%	28%	7.5%
Change in central retinal thickness (CRT) as assessed by OCT (± SD)*	-183±154 micrometre	-192±150 micrometre	-73±177 micrometre	-66±139 micrometre

*$p<0.0001$ for aflibercept groups compared to laser photocoagulation
**$p<0.01$ for aflibercept groups compared to laser photocoagulation

Week 100 results have also been reported for both studies. BCVA continues to be significantly improved in the aflibercept groups compared with the laser photocoagulation groups.[3,4]

The National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) near activities and distance activities subscales were used to assess patient reported outcomes. At 52 weeks, the results for the NEI VFQ-25 near activities subscale were significantly better for the aflibercept four-weekly group compared with the laser photocoagulation group in the VISTA study only, p=0.0168. There were no significant differences reported between the aflibercept eight-weekly group (the licensed dose) and the laser photocoagulation group in either study.

Summary of evidence on comparative safety

The proportion of patients experiencing ocular and non-ocular adverse events was similar across the treatment groups in the integrated safety analysis set for the VIVID and VISTA studies.[2] At least one ocular adverse event occurred in 59%, 58% and 64% of patients in the aflibercept four-weekly, aflibercept eight-weekly and laser photocoagulation groups, respectively. At least one non-ocular adverse event occurred in 75%, 76% and 74% of patients in the aflibercept four-weekly, aflibercept eight-weekly and laser photocoagulation groups, respectively.

There were no clinically relevant differences between the treatment groups in terms of serious ocular and non-ocular adverse events; 1.7%, 1.7% and 4.2% of patients in the aflibercept four-weekly, aflibercept eight-weekly and laser photocoagulation groups reported a serious ocular adverse event and 23%, 22% and 23% of patients in the aflibercept four-weekly, aflibercept eight-weekly and laser photocoagulation groups reported a serious non-ocular adverse event, respectively.

Adverse events associated with the injection procedure were more common in the aflibercept groups, e.g. conjunctival haemorrhage was reported by 31% of patients in the aflibercept four-weekly group, 25% of patients in the aflibercept eight-weekly group and 17% of patients in the laser photocoagulation group. Adverse events associated with disease worsening were more common in the laser photocoagulation group, e.g. abnormal visual acuity test was reported by 8.0% of patients in the laser photocoagulation group compared with 2.1% of patients in the aflibercept four-weekly group and 3.1% of patients in the aflibercept eight-weekly group.

Occurrence of arterial thromboembolic events was low and similar across the treatment groups: 3.1%, 3.5% and 2.8% of patients in the aflibercept four-weekly, aflibercept eight-weekly and laser photocoagulation groups, respectively.

Summary of clinical effectiveness issues

Aflibercept is the second medicine to be licensed for intravitreal use for the treatment of visual impairment due to DMO. Ranibizumab was accepted by SMC for restricted use in adults with BCVA of 75 ETDRS letters or less at baseline. The submitting company has requested that SMC considers aflibercept when positioned for use in the treatment of visual impairment due to DMO in adults with BCVA of 75 ETDRS letters or less at baseline.

In the VISTA and VIVID studies, patients in the aflibercept groups had a significantly greater improvement in BCVA at 52 weeks compared with laser photocoagulation with a similar rate of adverse events. Evidence beyond one year of treatment is limited. Both studies are planned to continue for three years and initial week 100 results support a sustained significant improvement in aflibercept treated patients compared with laser photocoagulation.[3,4]

Neither study was conducted in the UK. VISTA was conducted entirely in the United States and VIVID included patients from Europe. The baseline characteristics appear similar to patients who would be treated in clinical practice in Scotland. Most patients in the studies had type II diabetes; therefore, there is limited evidence for patients with type I diabetes.[1]

Laser photocoagulation was the mainstay of treatment for DMO prior to the use of intravitreal VEGF-inhibitors. The aim of treatment was to prevent visual loss whereas the aim of treatment with VEGF-inhibitors is to improve BCVA. Efficacy of laser photocoagulation in clinical practice is less than in clinical studies; this is thought to be due to a number of factors including laser equipment, patient factors and the laser operator. Aflibercept has not been studied in combination with laser photocoagulation.

Patient reported outcomes were assessed using NEI VFQ-25 near and distance subscales. There were no significant differences reported between the aflibercept eight-weekly group (the proposed licensed dosing schedule) and the laser photocoagulation group in either study. NEI VFQ-25 assesses binocular vision so results are likely to be reflective of the better seeing eye. Generally the patient's worse seeing eye was treated in the studies.

Clinical experts consulted by SMC advise that the current standard of care in Scotland is intravitreal ranibizumab. As there is no direct evidence comparing aflibercept with ranibizumab, the submitting company presented Bucher indirect and Bayesian mixed treatment comparison (MTC) analyses (fixed and random effects) in patients with DMO comparing aflibercept with ranibizumab. Four studies were included in the Bucher indirect comparisons and up to 10 studies (depending on the outcome) in the Bayesian MTC. Efficacy outcomes assessed were:

- Change from baseline in BCVA at 12 months
- Proportion of patients gaining ≥10 ETDRS letters of BCVA from baseline at 12 months
- Proportion of patients gaining ≥15 ETDRS letters of BCVA from baseline at 12 months
- Proportion of patients losing ≥10 ETDRS letters of BCVA from baseline at 12 months
- Proportion of patients losing ≥15 ETDRS letters of BCVA from baseline at 12 months

Bucher indirect comparison and MTC analyses were also presented for all serious adverse events, all serious ocular adverse events, all serious non-ocular adverse events, all adverse events, all ocular adverse events, all non-ocular adverse events, eye pain, hypertension, cataract and all-cause mortality at 12 months. There was evidence to suggest that aflibercept was superior to ranibizumab in the outcome change from baseline in BCVA at 12 months in both the Bucher indirect comparison and MTC analyses. The MTC fixed effects model provided evidence to suggest that aflibercept was superior to ranibizumab by reducing the proportion of patients with a loss of ≥10 ETDRS letters from baseline at 12 months; however, there was no evidence of a difference in the random effects model. As there was likely to be significant heterogeneity within the MTC due to the dissimilar baseline characteristics in the included studies, random effects would be preferred. There was no evidence of a difference between aflibercept and ranibizumab for the outcomes, proportion of patients gaining ≥10 ETDRS letters or gaining or losing ≥15 ETDRS letters from baseline at 12 months. There was no evidence of a difference in any of the safety outcomes between aflibercept and ranibizumab. As some of the studies were only published in abstract form, it was difficult to compare the baseline characteristics, adding uncertainly to the credibility of the analyses.

Clinical experts consulted by SMC considered that the introduction of this medicine may have a positive impact on service delivery due to the eight-weekly injection schedule.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing aflibercept to ranibizumab in patients with visual impairment due to DMO. For completeness, comparison versus laser photocoagulation was provided and served as a baseline analysis. Ranibizumab has been confirmed as an appropriate comparator by SMC clinical experts.

The company submitted a lifetime Markov state transition model in which patients moved according to their BCVA over time. BCVA is divided into eight categories or health states, each defined by 10 letters on the ETDRS scale. Patients were treated either in their study eye or fellow eye. The model structure consisted of three phases including the efficacy phase (to 16 weeks from the start of treatment), the maintenance phase (to 5 years from the start of treatment), and the 'rest of life' phase. Patients' vision could improve, remain the same or decline.

The clinical data used to support the comparison with laser came from two randomised controlled studies VIVID and VISTA which compared aflibercept to laser photocoagulation.

For the more relevant comparison with ranibizumab, the results of the MTC were used, although in some cases individual parameter estimates were taken direct from the RESTORE trial of ranibizumab (such as treatment discontinuation rate). The MTC indicated that aflibercept was superior to ranibizumab in terms of BCVA mean change from baseline. However, the submission also included differences in clinical endpoints in the economic model that were not statistically significant.

A range of costs was included in the analysis including drug acquisition costs, monitoring and administration costs, adverse event costs and the cost of blindness. A patient access scheme (PAS) is in place in NHS Scotland for ranibizumab and was incorporated into the analysis as the relevant price for ranibizumab. In the first year of treatment aflibercept was associated with a slightly higher number of injections versus ranibizumab (8 vs.7.93 for aflibercept and ranibizumab respectively based on the integrated VIVID/VISTA studies) and a lower number of total hospital visits (8 vs.12 for aflibercept and ranibizumab respectively). In years 2-5, the same number of injections and monitoring visits were applied to each arm of the model.

Utility values were taken from a published study which used the time trade off method. EQ-5D data were collected in the VIVID and VISTA studies, however these were considered to be relatively insensitive and therefore were not used in the base case but were provided in the scenario analysis.

A Patient Access Scheme (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 given on the price of the medicine. With the PAS, aflibercept was dominant versus ranibizumab resulting in lower total costs and a higher number of QALYs.

Results of the one-way sensitivity analysis with the PAS indicated that aflibercept remained dominant when the time horizon was reduced to 10 years and 5 years. A number of scenario analyses were also submitted by the company which tested alternative utility values, variation in the duration of the maintenance phase, equivalent unit costs and equivalent efficacy between treatments. When both treatments are assumed to have the same efficacy i.e. probability of patients gaining or losing ≥10 or

≥15 ETDRS letters is the same in both treatment arms, aflibercept with the PAS remained dominant versus ranibizumab.

The key weakness with the analysis was that the company included a number of non significant results i.e. the probability of gaining more than 10 letters, gaining more than 15 letters and losing more than 15 letters. A revised analysis which removed the non-significant differences and assumed no difference in efficacy resulted in savings versus ranibizumab of £1,472 with the PAS.

In summary, when comparable efficacy was assumed aflibercept remained cost-saving and therefore the economic case has been demonstrated.

*Other data were also assessed but remain commercially confidential.**

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 for Blind People and the Macular Society, which are both registered charities.

- RNIB has received funds from the pharmaceutical industry in the past two years, including from the submitting company. The Macular Society has received no funding from the pharmaceutical industry.

- Diabetic macular oedema is a complication of diabetes which affects the central vision. If not effectively treated it has a big impact on the day-to-day lives of patients, carers and their families, which may include: loss of employment and income, loss of independent mobility, increased living costs, increased risk of accidents, dependence on others, loss of self-esteem, social isolation, depression, and general difficulties with everyday life, in particular for this condition, managing glucose levels.

- Advantages of the new medicine include: a fixed dosing regimen which means that patients and their carers know when an injection will be administered, increased patient choice which can save a person's sight if they do not respond to current treatment.

- Aflibercept is a safe and effective treatment for diabetic macular oedema that will be particularly beneficial to patients who have not responded to currently approved treatments.

Additional information: guidelines and protocols

The Royal College of Ophthalmologists Diabetic Retinopathy Guidelines were updated in July 2013. Focal and focal/grid laser photocoagulation was previously the standard treatment for diabetic macular oedema. Growing evidence suggests that intravitreal VEGF-inhibitors (with or without laser photocoagulation) are superior to laser photocoagulation alone with better visual outcomes and the potential to improve visual acuity. They are therefore now considered the gold standard for patients with centre-involving diabetic macular oedema and reduced vision. Future studies will help to identify the best way to use these medicines in future.

The Scottish Intercollegiate Guidelines Network published SIGN 116: Management of diabetes in March 2010. This recommends that grid laser photocoagulation should be used for diabetic patients with clinically significant macular oedema in the absence of significant macular ischaemia. This guideline pre-dates the licensing of intravitreal VEGF-inhibitors.

Additional information: comparators

Intravitreal ranibizumab

Cost of relevant comparators

Drug	Dose Regimen	Cost in first year (£)
Aflibercept	**2mg intravitreal injection once a month for five consecutive doses, followed by one injection every two months. After the first 12 months the treatment interval may be extended based on visual and anatomical outcomes.**	**6,528**
Ranibizumab*	0.5mg intravitreal injection once a month until maximum visual acuity is achieved. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed when monitoring indicates loss of visual acuity due to DMO.	5,195

Doses are for general comparison and do not imply therapeutic equivalence. Costs do not take any patient access schemes into consideration. Costs from eMIMS on 28 July 2014. *Annual cost for ranibizumab based on mean of seven injections used in RESTORE study over the first 12 months. Data reporting follow up to 2 years suggest that the number of injections in the second 12 months is approximately three to four injections.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 3,897 in year 1 rising to 5,224 in year 5, with an estimated uptake rate of 10% in year 1 and 20% in year 5. The company has also estimated that there will be a discontinuation rate of 0.01% in all years.

Without PAS:
The gross impact on the medicines budget was estimated to be £2.44m in year 1 and £2.96m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact was estimated to be £249k in year 1 and £285k in year 5. It should be noted the budget impact estimates do not include either the aflibercept or ranibizumab PAS prices.

*Other data were also assessed but remain commercially confidential.**

References

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

1. Aflibercept solution for injection (Eylea®). Summary of product characteristics. Bayer Pharma AG. Electronic Medicines Compendium www.medicines.org.uk Last updated 21 August 2014.

2. Korobelnik J-F, Do DV, Schmidt-Erfurth U et al. Intravitreal Aflibercept for Diabetic Macular Edema. Ophthalmology 2014;-:1e8

3. Regeneron Pharmaceuticals, Inc. Diabetic Eye Remedy Drug Impresses in phase 3 trial. Press Release. 10 February 2014. http://www.biospace.com/News/regeneron-pharmaceuticals-inc-s-diabetic-eye/323285/source=TopBreaking

4. Regeneron Pharmaceuticals, Inc. (REGN) Release: Two-year results from phase 3 VIVID-DME trial of EYLEA® (aflibercept) injection for the treatment of diabetic macular edema show sustained improvement in vision. Press Release 19 July 2014. http://www.biospace.com/News/regeneron-pharmaceuticals-inc-release-two-year/340258/source=MoreNews

5. The Royal College of Ophthalmologists. Diabetic Retinopathy Guidelines - December 2012 (minor update June 2013). 2012

6. Scottish Intercollegiate Guidelines Network. SIGN 116: Management of diabetes. March 2010

This assessment is based on data submitted by the applicant company up to and including 12 September 2014.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

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.