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. (1186/16)
Bayer plc

09 September 2016

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 40mg/mL solution for injection (Eylea®) is accepted for use within NHS Scotland.

Indication under review: for adults for the treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV).

In a phase III, randomised, sham-controlled study in adults with myopic CNV, aflibercept was statistically superior to sham at improving visual acuity at 24 weeks.

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 in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

For adults for the treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV).

Dosing Information

A single intravitreal injection of 2mg aflibercept (equivalent to 50 microlitres). Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease. The schedule for monitoring should be determined by the treating physician. The interval between two doses should not be shorter than one month. Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (eg eye pain, redness of the eye, photophobia, blurring of vision) without delay. Each vial should only be used for the treatment of a single eye.

Product availability date

28 October 2015

Summary of evidence on comparative efficacy

Pathologic myopia or high myopia (defined as refractive error ≥ -6 diopters) is a leading cause of blindness, and choroidal neovascularisation (CNV) is one of the most common vision-threatening complications of the condition. Active myopic CNV is associated with elevated levels of vascular endothelial growth factor (VEGF) in the aqueous humour of the affected eye(s). Aflibercept is a human recombinant fusion protein that acts as a soluble decoy receptor to bind and inactivate VEGF-A. It subsequently inhibits neovascular growth and associated exudation, and has an immediate and direct beneficial effect on vision.[1,2] Aflibercept is also licensed for the treatment of neovascular (wet) age-related macular degeneration, visual impairment due to macular oedema secondary to retinal vein occlusion and visual impairment due to diabetic macular oedema. These indications have been reviewed separately by SMC.

MYRROR was a phase III, randomised, multicentre, double-masked, sham-controlled study to evaluate the efficacy, safety and tolerability of intravitreal aflibercept in adults with myopic CNV. The study was conducted for 48 weeks and recruited adults (aged ≥18 years) with high myopia (≥ -6.0 diopters or axial length of ≥26.5mm), active subfoveal or juxtafoveal myopic CNV, and a best-corrected visual acuity (BCVA) of 73 to 35 letters (Early Treatment Diabetic Retinopathy Study [ETDRS] equivalent of 20/40 to 20/200) in the study eye at 4 metres. A total of 122 patients were randomised in a 3:1 ratio to receive intravitreal aflibercept (n=91) or sham injection (n=31), stratified by country. Those allocated to aflibercept received one 2mg injection at baseline. Further 2mg 'retreatment' injections could be administered at a maximum frequency of once every four weeks through to week 44 if there was persistence or recurrence of CNV, ie if patients displayed at least one of the following criteria: (1) reduction in visual acuity (VA) by ≥5 letters from the previous ETDRS examination; (2) increase in central retinal thickness (CRT) >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 their clinical impression or diagnostics performed in the context of standard medical care.

Those patients who did not meet the retreatment criteria received sham injections only for the purpose of masking. In the sham group, patients received one sham injection at baseline and every four weeks through to week 20 regardless of retreatment criteria. At week 24 (after primary efficacy outcome assessment), patients received a mandatory intravitreal aflibercept 2mg injection, followed by further 2mg injections at a maximum frequency of once every four weeks through to week 44 if patients met the retreatment criteria.[3]

The primary efficacy outcome was the mean change in BCVA (as measured by ETDRS) from baseline to week 24. Assessment was performed using the last observation carried forward (LOCF) approach in the full analysis set (FAS), which comprised all randomised patients who received at least one study injection, and had a baseline and at least one valid post-baseline assessment of BCVA. The results demonstrated a significantly greater improvement in BCVA in the aflibercept group with a gain of 12.1 ETDRS letters, compared with a loss of 2 ETDRS letters in the sham group; treatment difference (least squares mean change) 14.1 ETDRS letters (95% confidence interval [CI]: 10.8 to 17.4), p<0.0001. The confirmatory secondary endpoint was the proportion of patients who gained ≥15 ETDRS letters at week 24, and this was achieved by a significantly greater proportion of patients in the aflibercept group (39% [35/90]) compared with the sham group (9.7% [3/31]); treatment difference (Cochran-Mantel-Haenszel-adjusted) 29% (95% CI: 14.4 to 44.0), p=0.0001. Exploratory analyses of these outcomes at week 48 demonstrated nominally significant improvements in the aflibercept group compared with the sham group. A significant improvement was seen for the mean change in CRT (exploratory endpoint, FAS, LOCF) in the aflibercept group compared with sham from baseline to week 24 (p<0.0001), though the result was not significant at week 48 (p=0.06). Nominally significant improvements in the aflibercept group compared with the sham group from baseline to weeks 24 and 48 were also demonstrated for the mean change in CNV lesion size and leakage from CNV (assessed as exploratory endpoints, FAS, LOCF).[3,4]

Aflibercept, compared with sham, was associated with statistically significant and clinically meaningful improvements in the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) total score and EuroQol-5 Dimension (EQ-5D) score from baseline to week 48.[2,4]

Summary of evidence on comparative safety

In the MYRROR study, treatment-related, treatment-emergent adverse events (TEAE) (up to 48 weeks) were reported in 9.9% (9/91) and 6.5% (2/31) of patients in the aflibercept and sham groups, respectively. Serious adverse events were reported in 7.7% (7/91) and 3.2% (1/31) of patients in the respective groups; however, in only one patient (in the aflibercept group) was this considered to be treatment-, injection- or procedure-related. Treatment-related ocular TEAE on the study eye were reported in 6.6% (6/91) of patients in the aflibercept group and in 3.2% (1/31) of patients in the sham group, and treatment discontinuation through week 48 as a result of an adverse event occurred in 5.5% (5/91) and 6.4% (2/31) of patients in the respective groups.[2,3]

The most commonly reported ocular TEAE were conjunctival haemorrhage (11% in the aflibercept group versus 3.2% in the sham group), eye pain (7.7% versus 3.2%), punctate keratitis (6.6% versus 13%), and dry eye (2.2% versus 6.5%). The most common non-ocular TEAE were nasopharyngitis (19% versus 9.7%), nausea (7.7% versus 0%), headache (6.6% versus 3.2%), and dizziness (5.5% versus 0%).[2]

Case reports of cerebral haemorrhage, hypertension and macular hole prompted the Committee for Medicinal Products for Human Use (CHMP) to request close monitoring of these adverse events in the periodic safety update reports; however, the European Public Assessment Report concluded that no new safety concerns arose with aflibercept for the treatment of myopic CNV compared to its existing

indications, and patients would be expected to receive fewer aflibercept injections compared to the other target populations.[2]

The aflibercept summary of product characteristics (SPC) notes that intravitreal injections have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract, and increases in intraocular pressure (within one hour of injection). Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported, and there are limited safety data in the treatment of patients with myopic CNV with a history of stroke, transient ischaemic attacks or myocardial infarction within the previous six months. The safety and efficacy of aflibercept therapy administered to both eyes concurrently has not been systematically studied, and bilateral treatment at the same time could lead to increased systemic exposure and adverse events. As with all therapeutic proteins, there is a potential for immunogenicity.[1]

Summary of clinical effectiveness issues

Within five to ten years of onset of myopic CNV, most eyes will progress to 20/200 or worse, and patients will progressively lose visual acuity at a rate of approximately 10 to 15 letters (2 to 3 lines) over two years. Current treatments include verteporfin photodynamic therapy (vPDT) and ranibizumab. Data suggest that photodynamic therapy may reduce the risk of visual loss compared to placebo; however it has not been shown to improve mean visual acuity. Ranibizumab was the first licensed exclusively pharmacological therapy (VEGF-A inhibitor) for the treatment of visual impairment due to CNV secondary to pathologic myopia, demonstrating improved and sustained visual acuity compared with vPDT.[2,5] Ranibizumab was accepted for use within NHS Scotland by SMC in 2013 and clinical experts consulted by SMC suggest that it is the most relevant comparator.

MYRROR demonstrated that aflibercept was statistically superior to sham for both the primary and key secondary endpoints, with clinically meaningful improvements in visual acuity sustained through week 48. Throughout the study, patients in both groups received a median of three aflibercept injections (mean 4.2 in the aflibercept group and mean 3.0 in the sham group). Most aflibercept injections were administered during the first eight weeks of the aflibercept treatment phase in both groups, with minimal need for retreatment. In the aflibercept group, 14% (13/90) of patients only required one injection during the study, suggesting that for some patients the disease may be controlled with a single injection. It was observed that an increased number of injections over the 24 or 48 weeks only provided limited gains in visual acuity. From week 4, a rapid increase in BCVA was observed in the aflibercept group and this continued through week 24, and was then maintained or slightly improved from week 24 to 48. Patients in the sham group received intravitreal aflibercept from week 24 and improvements in visual acuity were demonstrated with a mean gain of 5.9 letters from week 24 to 48. Compared with the aflibercept group, who gained a mean of 12.1 letters in the first 24 weeks of treatment, the improvements in the sham group were less marked in the first 24 weeks of aflibercept treatment, suggesting that patients may benefit from early initiation of treatment, and there may be irreversible damage if myopic CNV is left untreated.[2,3]

All patients in the study were of Asian ethnicity so conclusions about efficacy in the European population could not be drawn from the study alone. The submitting company conducted an evaluation of the ethnical insensitivity of aflibercept in Asians and Whites in order to justify extrapolation of the data from MYRROR to other ethnicities and geographic regions, in particular, European patients. Clinical studies conducted with aflibercept for other approved indications were included in the main analysis, and comparative efficacy results were based on improvements in BCVA and CRT. In general, similar efficacy trends in the absolute treatment differences were observed between Asians and Whites, which was confirmed by consistent overlap of the corresponding 95% CIs. The CHMP

therefore agreed that the results of the study could be extrapolated to the European population, though the SPC notes that there is no experience for aflibercept in the treatment of non-Asian patients for the indication under review.[1,2]

As the experience with intravitreal aflibercept in myopic CNV was limited to only a small number of patients for up to 48 weeks in the MYRROR study, the long-term effects on visual acuity and safety are currently unknown.[3] The submitting company proposes to enrol patients with myopic CNV in the planned observational post-authorisation safety study (PASS), that is designed to gain real-world clinical experience of aflibercept use in Europe.[2] There is no experience of using aflibercept in those who have previously undergone treatment for myopic CNV, and in those with extrafoveal lesions.[1]

In the absence of study data for aflibercept relative to an active comparator, the submitting company presented a Bayesian network meta-analysis (NMA), comprising three studies, which compared aflibercept with ranibizumab, vPTD and placebo for the treatment of adults (aged ≥18 years) with myopic CNV. The outcome assessed was the three-month mean change from baseline in BCVA, and the results demonstrated that aflibercept was similar to ranibizumab and superior to placebo and vPDT. The NMA was limited by heterogeneity across the study populations (eg stage of disease and previous treatments), the 'placebo' groups (eg sham intravitreal injection versus dextrose 5% intravenous infusion plus laser), and outcome data measures (eg mean versus medians, and ETDRS letters versus lines). There was also a lack of comparison of efficacy variables other than BCVA (e.g. central retinal thickness or assessment of lesions). Safety and quality of life were not compared.

Clinical experts consulted by SMC consider that the place in therapy of aflibercept is as an alternative to ranibizumab.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing aflibercept to ranibizumab in adult patients with visual impairment due to myopic CNV. The time horizon for the analysis was over a life time with initial treatment given in years 1 and 2 of the analysis (recurrence and fellow eye involvement could arise in later years). SMC clinical experts have confirmed that ranibizumab is the appropriate comparator.

Aflibercept and ranibizumab were assumed to have similar clinical outcomes on the basis of the NMA discussed above. Adverse events were assumed to be identical. The only costs in the analysis related to the acquisition costs of aflibercept and ranibizumab. No additional costs of treatment administration or monitoring were included on the basis that it was assumed that both treatments would require the same number of injections of 4.2 in year 1 and 1 in year 2. Fellow-eye involvement and recurrence costs were also included but again, the rates were assumed to be equivalent between treatments.

A patient access scheme (PAS) was submitted by the company and was 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 price of the medicine.

With the PAS, the results indicated that over a lifetime, aflibercept would be associated with savings of £178 per patient. A PAS is in place for ranibizumab and this was included by using an estimate of the relevant price for ranibizumab.

The key uncertainties related to:

- The cost minimisation analysis was underpinned by an NMA which has a number of weaknesses.
- The analysis assumed that aflibercept and ranibizumab would require the same number of treatments. Data from the RADIANCE study for ranibizumab showed that in the disease activity group, ranibizumab required a mean number of injections of 3.5 in year 1 and in the visual acuity stabilisation group, a mean number of injections of 4.6 in year 1. The company provided analysis where it was assumed that ranibizumab would require 3.5 injections compared to 4.2 for aflibercept, to correspond to the levels reported in the respective pivotal studies for ranibizumab (disease activity arm) and aflibercept. With the PAS, this showed that aflibercept would no longer be the cost-minimising treatment with incremental costs of £298 over the lifetime horizon. However, SMC clinical experts were asked to comment on the assumption of equal numbers of injections and the responses to date provided reassurance that the base case assumption was reasonable.
- The analysis did not include any allowance for treatment monitoring on the basis that this would be the same between aflibercept and ranibizumab and also assumed equivalence in terms of recurrence rates. SMC experts were asked to comment on these assumptions and the responses confirmed that they were reasonable.

Despite these issues, the economic case was considered 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 Group.

- We received a patient group submission from Royal National Institute of Blind People (RNIB Scotland), which is a registered charity.

- RNIB Scotland has not received any pharmaceutical company funding in the last two years.

- Choroidal neovascularisation associated with pathological myopia (mCNV) is a sight threatening condition with associated loss of depth perception, central vision and the potential to develop cataracts. It commonly develops at a young age (40-60 years) compared to other sight threatening conditions. This devastates lives and has a negative impact on financial and social independence, mobility and mental health. Loss of sight results in increased dependency on family and carers, and often carers need to give up work as the burden of their caring role increases.

- Currently only one intravitreal treatment for mCNV is available. Another treatment option would be of benefit to increase the potential of an effective treatment for people living with this debilitating condition.

- Aflibercept may prevent avoidable sight loss. This effective treatment can result in getting back to or staying in work which would have a huge impact of self-esteem, independence and income.

Additional information: comparators

The most relevant comparator is ranibizumab. Verteporfin photodynamic therapy (vPDT) is also available for use.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Aflibercept	**Single 2mg intravitreal injection; further injections of 2mg may be administered at monthly intervals if the disease persists**	**3,264***
Verteporfin	6mg/m^2 body surface area by intravenous infusion	2,550 to 3,400**
Ranibizumab	Single 0.5mg intravitreal injection; further injections of 0.5mg may be administered at monthly intervals if the disease persists	1,653 to 2,204***

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online 06/07/16. Costs are based on treatment of one eye. Costs do not take any patient access schemes into consideration.
*Cost based on 4 doses of aflibercept (mean number of doses in MYRROR study [aflibercept group] was 4.2).
**Cost based on a range of 3 to 4 verteporfin treatments in an adult with body surface area 1.8m^2 (mean number of treatments in first year was 3.5 according to the Visudyne® summary of product characteristics, last updated 17/12/15); cost of photodynamic therapy not included.
***Cost based on a range of 3 to 4 doses of ranibizumab (mean number of doses in RADIANCE study [disease activity group] was 3.5).[5]

Additional information: budget impact

The submitting company estimated there would be 304 patients eligible for treatment with aflibercept in year 1 and 1,520 patients in year 5, to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

References

The undernoted references were supplied with the submission.

1. Bayer plc. Aflibercept 40mg/mL solution for injection (Eylea®). Summary of product characteristics. Date of revision of the text: 11/2015.

2. European Medicines Agency. European Public Assessment Report: aflibercept. EMA/758988/2015. 24 September 2015.

3. Ikuno Y, Ohno-Matsui K, Wong T-Y, Korobelnik J-F, Vitti R, Li T, et al. Intravitreal aflibercept injection in patients with myopic choroidal neovascularization: The MYRROR study. Ophthalmology 2015;122(6):1220-7.

4. NCT01249664. VEGF Trap-eye in choroidal neovascularization secondary to pathologic myopia (mCNV) (Myrror) www.clinicaltrials.gov (accessed 07/06/16).

5. Scottish Medicines Consortium (SMC) advice on ranibizumab (Lucentis®). SMC drug ID 907/13. Date Advice Published: 11 November 2013.

This assessment is based on data submitted by the applicant company up to and including 11 August 2016.

**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.