Overview - Bayer response to ACD for aflibercept DMO

We welcome the preliminary guidance from NICE to recommend aflibercept as an option for the treatment of visual impairment caused by diabetic macular oedema (DMO) for eyes with a baseline central retinal thickness (CRT) of 400 micrometres or more.

However, aflibercept is a clinically and cost effective option for all patients with visual impairment due to DMO including those with a baseline CRT of under 400 micrometres and there is an unmet need for safe and effective treatments in these patients. Our key points are as follows:

- **The evidence of the supremacy of aflibercept compared with ranibizumab in terms of mean change in best correct visual acuity (BCVA) from baseline has not been adequately considered by the Appraisal Committee**
- **The ERG base case, upon which the recommendations have been based, includes several assumptions that are not supported by robust evidence or adequate justification. The amendment of these assumptions to provide a more robust base case would indicate that aflibercept is a cost effective use of NHS resources in all patients with visual impairment due to DMO assuming a threshold of £20,000-£30,000 per QALY gained.**
- **In patients with a baseline CRT of less than 400 micrometres, it has been highlighted that current standard of care has evolved and that clinicians watch and wait to treat with ranibizumab when the CRT reaches the 400 threshold defined by previous NICE guidance (TA274). Consideration of a comparison versus watch and wait indicates an improved cost effectiveness profile for aflibercept in that subgroup.**

Q1. HAS ALL OF THE RELEVANT EVIDENCE BEEN TAKEN INTO ACCOUNT?

Significantly greater mean change in visual acuity with aflibercept compared with ranibizumab

In their consideration of the evidence (section 4.6), the Appraisal Committee have not fully considered the results of the indirect comparison and network meta-analysis that reported a (statistically) significantly better efficacy result with aflibercept compared with ranibizimab in terms of mean change in BCVA from baseline to 52 weeks.

Q2. ARE THE PROVISIONAL RECOMMENDATIONS SOUND AND A SUITABLE BASIS FOR GUIDANCE TO THE NHS?

The recommendations have been based on the results of the ERG economic base case. The following aspects of the ERG base case are insufficiently robust in terms of the evidence available and there is inadequate justification for the inputs and assumptions used:

Issue 1: Inconsistent use of clinical trial evidence to source resource use inputs and assumptions in year 1

The ERG indicated that the clinical trial data, as opposed to evidence of expected or current resource use, should be used as the source of resource use inputs and assumptions in the economic model. However, this approach was not applied consistently in the ERG base case. Moreover, this approach is only relevant where treatment effect and safety inputs are also taken from those clinical trials (i.e. in year 1 alone).

Administration and monitoring with laser in year 1

The number of laser administrations in the included clinical studies in year 1 was based on monthly monitoring visits. This was also the case in the included ranibizumab studies where the decision to administer an injection was based on monthly monitoring in the first year. Therefore, the number of administrations and the associated efficacy from the included clinical studies was based on frequent monitoring. In VIVID and VISTA, aflibercept was administered according to a fixed regimen and was not determined by monthly monitoring visits.

Number of ranibizumab injections in year 1

The ERG excluded a key study, DRCR.net Protocol I, when estimating the number of ranibizumab injections in the first year. Whilst we accept that it is not ideal to mix mean and median estimates, the exclusion of a key study in the network meta-analysis from the estimate adds uncertainty to the estimate of 7.43 used by the ERG in their base case (DRCR.net Protocol I reported a median of 9 injections).

Issue 2: Inappropriate resource use inputs and assumptions in year 2

Efficacy data from clinical studies were not used in year 2 in the ERG base case. This was mainly due to the fact that it was not possible to conduct an indirect comparison of aflibercept versus ranibizumab in year 2 due to the confounding aspect of additional treatment administered in the clinical studies. Therefore, resource use inputs from clinical studies are less relevant from year 2 onwards.

Number of injection visits assumed for aflibercept in the revised ERG base case in year 2

The ERG estimated 5.45 injections in the 2nd year for aflibercept. This is not in line with the Summary of Product Characteristics (SmPC) for aflibercept, the presented data from VIVID/VISTA, clinical opinion, and is an overestimate of the number of injections in year 2.

- The SmPC posology for aflibercept differs to the treatment protocol in VISTA and VIVID beyond week 52. The trial protocols specified a bi-monthly treatment regimen in year 2. The SmPC describes a treat-and-extend dosing regimen, so that bi-monthly treatment intervals may be extended after the first year. This would lead to potentially fewer aflibercept injections in expected UK clinical practice than those reported in the clinical trials.
    - *"After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and anatomic outcomes."*
- Moreover, the economic model does not include comparative efficacy data from the VIVID, VISTA or RESTORE trials in year 2 as an indirect comparison could not be conducted. Therefore, assumptions of equivalent efficacy for aflibercept and ranibizumab have been made in year 2. This means that the number of injections stated in clinical trials is not directly relevant to the other inputs assumed in the model in year 2. Given an assumption of equivalent efficacy, an assumption of equivalent injections would be more aligned, particularly given the significantly better results with aflibercept cited in our response to Q1.
- The figure used by the ERG is also not in line with the average mean number of active injections reported at week 100 from VIVID and VISTA (13.5 and 13.6 injections respectively) as presented in our submission (p194). Given the mean number of active injections at week 52 was 8.55, this leads to a difference of nearer 5 injections administered in year 2.
- The ERG also state that their estimate is likely to be an underestimate of number of aflibercept injections in year 2 as reporting from VISTA and VIVID was at week 100, not week 104. However, the ERG omits to mention that RESTORE also reported up to month 23.
- It is also inappropriate to compare the VISTA, VIVID, and RESTORE studies in year 2 as there is insufficient information on the RESTORE population to compare the studies. The reason for the non-enrolment of 63 patients in RESTORE in year 2 was 'not well documented' (Lang, et al. 2013)[1].

Number of laser visits in year 2

It was assumed in the model that 1 laser administration visit occurred in year 2 and patients stayed in the same health state that they were in at week 52. It should be noted that this was conservative given the comparative efficacy data in year 1 from VISTA and VIVID shows the superiority of aflibercept versus laser. Moreover, as presented in our submission (p61), 35-41% participants receiving laser in VIVID/VISTA received additional rescue treatment, including aflibercept, through to week 100 and these data (p100 of the submission) were excluded from the primary analysis that showed a mean change in BCVA of 0.7 to 0.9 letters to week 100 in VIVID and VISTA respectively.

Issue 3: Inappropriate estimate of the unit cost of laser administration visits

In previous appraisals, the administration cost of an injection has been costed at the same price as a laser visit. We heard anecdotally from several consultant ophthalmologists that a laser visit is

[1] Lang GE, et al. Two-Year Safety and Efficacy of Ranibizumab 0.5 mg in Diabetic Macular Edema. Interim Analysis of the RESTORE Extension Study. Ophthalmology 2013;120:2004e2012

actually charged at a higher cost in clinical practice than an injection visit. Unfortunately, NHS reference costs do not distinguish a laser administration cost.

- In turn, the ERG has included a lower cost for laser in their base case. This is based on feedback from one individual clinician who is based in Northern Ireland and may not fully represent all of England and Wales or clinical practice in general.
- The costs used in the concurrent appraisal of dexamethasone intravitreal implant for DMO were £116.68 for both laser and injection administration visits (monitoring was costed at £80.04, with £18.06 for an optical coherence tomography (OCT)).
- In addition, to note, the injection administration cost used in the submitted model (£196) included the cost of monitoring. This cost was based on that used by the ERG in NICE appraisal TA305 aflibercept for macular oedema secondary to central retinal vein occlusion (CRVO). An administration visit is assumed to include the cost of a monitoring visit and therefore the cost of an OCT is added to the baseline unit cost for administration. Therefore, to include the assumption that 50% of treatments are administered using a two-stop system (separate administration and monitoring) would double count the cost of monitoring visits.

Issue 4: Inappropriate estimate of fellow eye involvement using VIVID and VISTA data

It is not stated in the ERG report that the rate of fellow eye involvement was amended in the ERG base case. However, it appears that this was the case. The rate of fellow-eye involvement recommended by the ERG at baseline is inaccurate.

- Several epidemiology publications for DMO in the UK highlight that the number of people with clinically significant DMO is much lower than those with any form of DMO[2,3,4.]

Issue 6: Availability of shift tables from VIVID and VISTA

The ERG criticised the use in our submitted model of monthly transition probabilities based on the published data for VISTA and VIVID and stated that it would be more appropriate to use patient level data from VIVID and VISTA. This data was available in the submitted model versus laser. Individual patient data for ranibizumab is not available so the model versus ranibizumab was based upon the network meta-analysis data. However, the ERG decided not to use this data for the laser comparison and did not ask for clarification on using this data. Using this data improves the ERG base case versus laser.

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[2] Minassian, et al. Prevalence of diabetic macular oedema and related health and social care resource use in England. Br J Ophthalmol 2012;96:345e349. doi:10.1136/bjo.2011.204040,

[3] Keenan TDL, et al. United Kingdom National Ophthalmology Database Study: Diabetic Retinopathy; Report 1: prevalence of centre-involving diabetic macular oedema and other grades of maculopathy and retinopathy in hospital eye services, Eye (2013) 27, 1397–1404

[4] Scanlon PH, et al. Epidemiological Issues in Diabetic Retinopathy. Middle East Afr J Ophthalmol. 2013 Oct-Dec; 20(4): 293–300.

Other minor considerations

As stated in our response to the draft scope, the rates of glaucoma for aflibercept based on VIVID/VISTA were very low and it was not a particularly relevant outcome to include in the base case for aflibercept. However, there was a minor error in the glaucoma rates used in the submitted model. Removing the incorrect glaucoma rates from the economic model results in a small reduction in the total stated costs of aflibercept in our submitted base case by approximately £220.

INCORPORATING WATCH AND WAIT AS THE APPROPRIATE COMPARATOR FOR PATIENTS WITH CRT AT BASELINE OF <400 MICROMETRES

It was highlighted to the Appraisal Committee that laser is not the most appropriate comparator for the subgroup of DMO patients with a baseline CRT of less than 400 micrometres at baseline. Although not included in the scope for this appraisal, watch and wait was subsequently cited as the appropriate comparator. The ICER versus watch and wait would be considerably improved compared to that proposed by the ERG versus laser.

The Markov model has been designed with the scoped comparators, ranibizumab and laser, in mind. Therefore, at this stage, we cannot incorporate watch and wait into the current model without additional analysis. However, we have assessed the potential evidence available and made estimates of how this would improve the cost effectiveness profile of aflibercept in the <400 micrometres subgroup.

Whereas, for observation, the main cost would be regular monitoring, the cost for watch and wait would be monitoring and then adding on the cost of treatment when people qualify for treatment at a later time. One might imagine that the cost of treatment and administration is similar whether it is delivered immediately or delayed. There is no evidence at this point to suggest that treatment continues indefinitely or that survival times would affect the duration of treatment.

Assuming that monitoring takes place before and after treatment, cost of monitoring may be higher for those treated later rather than later as monitoring would be frequent enough to ensure immediate treatment when the NICE criteria are met.

Due to the recent introduction NICE guidance into UK clinical practice for DMO, there is a paucity of long term data to indicate the impact of delaying treatment on the efficacy and safety of treatments, in addition to the costs. Anecdotal evidence suggests that treating earlier is the most appropriate treatment strategy. Patients will have longer to benefit following treatment in the long term.

Q3. ARE THE SUMMARIES OF CLINICAL AND COST EFFECTIVENESS REASONABLE INTERPRETATIONS OF THE EVIDENCE?

We would like to highlight the following specific items from the ACD document cannot be considered a reasonable interpretation of the evidence:

The Technology

Section 2.3 – Description of posology

The ACD cites only part of the posology from the Summary of Product Characteristics (SmPC). The posology should be cited in full as follows to avoid misleading prescribing information:

- The recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitres.
- Eylea 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 with Eylea, 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, Eylea should be discontinued.

Clinical effectiveness

Section 3.4 – Description of subgroup data provided by the manufacturer

A subgroup analysis of the primary outcome was also provided (see page 335 of the original submission). Moreover, here and throughout the submission, the subgroup has been defined as greater than 400 micrometres. This should be 400 micrometres ***and greater***.

Section 3.9 – Description of network meta-analysis by the manufacturer

The description of the network meta-analysis does not mention the inclusion of the DRCR.net Protocol I study. Moreover, the ACD does not mention the limitations described in the submission with regard to the comparisons with corticosteroids. An indirect comparison with the pivotal MEAD study for dexamethasone was not possible as there was no common comparator.

Section 3.13 – Description of the SmPC

This section of the ACD provides an inaccurate description of the SmPCs for aflibercept and ranibizumab. We would recommend that this section be reworded in line with the wording of the SmPCs. The marketing authorisation for aflibercept specifies the fixed regimen of injections in the first year (8 injections). The SmPC does not mention injection visits doubling as monitoring visits. In addition, the revised SmPC for ranibizumab does not 'reduce the number of monitoring visits

needed'. The previous reference to monthly monitoring of visual acuity has been replaced with alternative wording.

The SmPC for aflibercept specifically states that no additional monitoring is required in year 1. This is not the case for ranibizumab. Aflibercept is associated with a pro-active fixed regimen in the first year whereas ranibizumab is associated with a reactive regimen based on monitoring.

In addition, the ERG's revised economic model uses number of injections from the clinical trials. The number of injections for ranibizumab in year 1 in the RESTORE, REVEAL, and DRCR.net studies was based on frequent monitoring. Therefore, it is appropriate, if using numbers of injections from the studies, to take account of this frequent monitoring in the trials. This was not the case in VISTA and VIVID where the fixed regimen in year 1 and 2 was protocol driven regardless of monitoring.

Cost effectiveness

Section 3.20 – Description of the ERG base case

It is inappropriate to use the phrase 'corrected errors identified during its critique of the model' as there remains uncertainty with the inputs and assumptions used by the ERG in their base case. Even the ERG in their report acknowledge that, in terms of the dosing rates in the second year, "It is possible that this is more a reflection of the differences between the trials than any difference that will apply in the real world" (p136).

It would be more appropriate to use 'The ERG built an exploratory base-case analysis using their preferred inputs and assumptions identified during the critique of the model…'
The ERG base case assumes 8.55 injections of aflibercept in the first year. This is higher than the anticipated number of aflibercept injections in clinical practice in the UK in year 1.

- Our submission stated that the number of aflibercept injections specified in the summary of product characteristics (SmPC) is 8 injections in the first year. The SmPC refers to 5 consecutive monthly monitoring visits followed by one injection every other month. There are 12 months in a calendar year. Therefore, this amounts to 8 injections in total according to the fixed regimen in the marketing authorisation.
- The treatment protocol in VISTA and VIVID studies varied slightly in comparison with the licensed posology as the clinical trial protocols specified 4-weekly and 8-weekly injections rather than monthly or bi-monthly.
- The ERG argued that the number of injections should be based on the clinical trial data. However, the ERG excluded information from a ranibizumab study to inform the estimated number of ranibizumab injections. The ERG excluded the median estimate of 9 injections from the DRCR.net Protocol I study on the basis that information was not available on the mean. The lowest estimate for the number of ranibizumab injections based on clinical studies has been used by the ERG.
- The SmPC incorporates a stopping rule if visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment. This would reduce the average number of injections in clinical practice, in addition to those discontinuing for other reasons, as already incorporated into the economic model.

Section 3.25, 4.5, 4.13 - Baseline CRT subgroup data

In B7, C6, C7, and C9 of the response to clarification, we provided extensive additional subgroup data, including risk ratios, to that provided in the original submission. These were provided both for the pooled VIVID and VISTA studies and for each study separately. We also provided a cost effectiveness analysis versus ranibizimab in the subgroup for 400 micrometres and over (page 337 of original submission).

It is inappropriate to use the following wording: *'there was no significant improvement over laser in visual acuity outcomes'.* Results indicate that improvements achieved with aflibercept over laser in vision and other outcomes were robust and similar regardless of baseline CRT.

The ERG raised the question of whether the VISTA study should be included in the base case and whether it was appropriate to pool data from VISTA and VIVID. The pivotal VISTA study is a relevant clinical study to the assessment of aflibercept as the marketing authorisation for aflibercept is the treatment of adults with visual impairment due to diabetic macular oedema (DMO) is not limited to a particular subgroup of patients or a particular line of therapy. Moreover, participants in the VISTA study would not differ particularly to those seen in clinical practice in the UK which would include those who have received a variety of prior treatments, treatment naïve patients, and patients with different levels of central retinal thickness. Ignoring the VISTA study would exclude a considerable piece of evidence from the appraisal.

Extensive data was provided both pooled and separately by individual study. As discussed in the ACD, about a quarter of the patients in the VISTA and VIVID study had a CRT of less than 400 micrometres at baseline. This was a post hoc sub-group analysis and, hence, the study was not designed specifically to assess this subgroup.

Q4. ARE THERE ANY ASPECTS OF THE RECOMMENDATIONS THAT NEED PARTICULAR CONSIDERATION TO ENSURE WE AVOID UNLAWFUL DISCRIMINATION FOR THE SPECIFIED GROUPS?

No equality issues with regard to this recommendation are known.