Issue 1 Number of aflibercept injections – year 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P5: The ERG suggests that Bayer has underestimated the number of aflibercept doses in the first year and that 8 rather than 7 would have been more reasonable.	Change to: The expected number of aflibercept injections, according to the summary of product characteristics (SmPC), is 7 in the first year.	The SmPC is unambiguous in its wording for the dosing regimen for aflibercept in the first year and specifically refers to months rather than weeks. The SmPC specifies three initial monthly doses of aflibercept followed by an aflibercept injection every other month. In the first year this equates to 7 injections. A month is equal to 28-31 days or 4.3 weeks, rather than, as suggested on p67, 4 weeks. The VIEW studies used a 4-weekly assessment schedule but did allow for a variation of up to 3 days from the 4 weekly assessment visit date. Therefore, the VIEW trial data included 7.7 injections of aflibercept in the first 52 weeks. Our submission base case, in line with the methods for technology appraisal, considers expected aflibercept use in line with the UK marketing authorisation for wet AMD. However, we did do a scenario analysis to consider the impact of using clinical trial data but this did not alter our overall	This also needs to be read in conjunction with the review of the number of aflibercept injections during the VIEW trials as per the ERG report Table 47 and subsequent text. In the light of this the ERG remains of the opinion that the most reasonable estimate for the first year is 8 injections. No revision required.

		conclusions regarding cost effectiveness of aflibercept.	

Issue 2 Use of LOCF analysis in VIEW 1 and VIEW 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P2: The ERG raised concern over the use of the last observation carried forward method (LOCF) method within VIEW 1 and VIEW 2 as it assumes stable disease which may not be appropriate for wet AMD	Add: However, an exploratory analysis by the ERG using observed data did not change the overall outcome of the indirect comparison.	LOCF is a standard method for accounting for missing data in randomised clinical trials. The quantity of missing data in the VIEW studies was low. The use of observed data did not change the overall conclusions in our submission. Clarifying the impact of using alternative methods of analysis will enable readers to understand its relevance in relation to the decision problem.	The ERG would suggest adding the following sentence: 'These analyses did not change the overall conclusion of the indirect comparison.'

Issue 3 Exclusion of 0.3mg arm of the DETAIL study from the network meta-analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P2: The ERG noted that an arm of the DETAIL study was omitted from the network meta-analysis.	Include: This arm from the DETAIL study investigated the 0.3mg dose of ranibizumab which is not licensed in the UK and therefore not directly relevant to the decision problem.	0.3mg is not a licensed dose for ranibizumab. Unlicensed doses were excluded from the analysis as the decision problem of interest related to 2mg aflibercept and 0.5mg ranibizumab,	Although we agree with the manufacturer's comment it is still unclear why they did include the 0.3mg arm in the network meta-analysis for the MARINA, PIER, EXICITE and EXTEND trials but not for the DETAIL trial. The ERG

		the doses licensed in the UK.	suggestion would be to replace the final sentence of section 1.3 with as follows: 'This arm from DETAIL, and indeed from MARINA, PIER, EXICITE and EXTEND investigated the dose of ranibizumab which is not licensed in the UK and therefore not directly relevant to the decision problem. However, as it was included in the network for MARINA, PIER, EXICITE and EXTEND, it should also be included for DETAIL to ensure the network was as complete as possible. For this reason the ERG undertook an analysis which included the 0.3mg arm for DETAIL.'

Issue 4 Modelling of the second eye in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P5: The ERG indicates that presentation of quality of life values related to binocular health states could have facilitated a	Clarification of the word 'correct'.	Modelling of the second eye involvement relied on a number of assumptions which simplified the description of treatment in the	The ERG remains of the opinion that the modelling of 2nd eye involvement is incorrect.

richer consideration of the impact of treatment upon vision if the approach adopted for the 2nd eye modelling would have been 'correct'.		second eye. While the ERG may believe that the simplification of the second eye modelling renders the results untenable, the assumptions used for the second eye modelling were stated in the submission document and clarified in response to ERG questions. The manufacturer believes the second eye modelling was not incorrect although it might be described as limited. Moreover, given that evidence of the relative and safety of treatments for wet AMD is based on the study eye alone, any modelling of the cost effectiveness of treatment of a second eye will be limited, based on assumptions, and subject to considerable uncertainty. The VIEW study protocols did not allow for fellow eyes with wet AMD to be treated with aflibercept. Therefore, given aflibercept is a new technology, there is currently no further evidence available for the clinical effectiveness of aflibercept in the fellow eye. Similarly, other RCTs included in the network meta-analysis do not provide evidence of clinical effectiveness for ranibizumab in the fellow eye such that it can be compared with aflibercept.	It is not just a matter of few simplifying assumptions but the fact that the modelling of 2nd eye involvement does not address fundamental issues such as the relative treatment effects of aflibercept and ranibizumab, or indeed any treatment effect for the 2nd eye. The modelling of 2nd eye involvement could have been rebuilt, with the proviso that the transitions in the first two years of treatment could have been translated into monthly TPMs (though if this is not possible then some further imagination could arrive at a means of modelling 2nd eye involvement). However, this is outside the ERG role. The ERG is bound by the model structure as submitted by the manufacturer. No revision required.

		It would be useful if the ERG would clarify the changes to the 2nd eye modelling that would have facilitated a richer consideration of the impact of treatment on vision and state the strengths and limitations of these changes.	

Issue 5 Spelling of pegaptanib

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P8: Incorrect spelling of 'pagaptanib'	Correct spelling of pegaptanib throughout document	In line with generic name.	Proposed revision accepted.

Issue 6 Exclusion of monitoring costs from conclusions of cost effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
P4, 6 and 7: The ERG indicates that a 40-50% PAS discount on the price of ranibizumab is sufficient for aflibercept to become more costly in terms of the direct drug and administration costs.	Add: However, this does not include monitoring costs which are an important aspect of the cost of managing wet AMD.	NICE, according to its methods of technology appraisal, considers all the relevant benefits and costs associated with a new technology. It is misleading to select particular costs to make conclusions about cost effectiveness, as this is not relevant to the overall decision problem where all costs will be considered. Our submission clearly states that a	While not a factual error, the summary section of page 5/6 does not have an immediate read across to the relevant table that highlights both the drug and the administration costs, and the monitoring costs. Revision required: Append "Though further cost

		key differentiator between aflibercept and ranibizumab is that the SmPC for aflibercept states that monitoring is not required in between every other month injections and allows for even less frequent monitoring after month 12. However, the SmPC for ranibizumab specifically indicates the need for monitoring of visual acuity each month. Our submission also highlights the capacity issues in the NHS associated with a requirement for monthly monitoring.	offsets from reduced monitoring costs for aflibercept are still anticipated" to "For the direct drug and administration costs of aflibercept to exceed those of ranibizumab" (two sentences"

Issue 7 Clarification on treatment effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P48: The ERG mentions that "… treatment effectiveness is based upon the relative risks estimated within the Kleijnen systematic review."	Change to: Treatment effectiveness for *ranibizumab* is based upon the relative risks estimated within the Kleijnen systematic review.	Effectiveness for aflibercept is based on the VIEW 2 trial data and not on the relative risks.	Proposed revision accepted.

Issue 8 Correction of "average administration" cost

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P54: The ERG reports the unit cost for "Average administration" at £275	Change to: £257.50	NHS reference costs: - Outpatient procedure: £79.74 - Day-case:402.08 Weighting based on 2010-11 HES: - Outpatient procedure: 44.87% - Day-case: 55.13% Resulting weighted average cost: £257.50	This is a typo and requires revision. Proposed revision accepted.

Issue 9 Addition to description of proportion of patients in one and two stop models in year 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P56: (Footer) The ERG comments that "from the electronic model it appears that in year 1 the proportion of one stop visits for aflibercept may be assumed to be 100% while the proportions for ranibizumab is assumed to be 50%.	Add: This is due to the fixed dose of aflibercept during the first year of treatment.	Aflibercept 2Q8 has a fixed dose during the first year and therefore it does not require a separate monitoring visit beforehand to determine if a dose is required or not.	As far as the ERG is aware, this assumption and the justification for it were not presented in the manufacturer submission. Nevertheless, it appears to be a reasonable argument. Proposed revision accepted.