National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Aflibercept solution for injection for the treatment of macular oedema caused by central retinal vein occlusion [ID578]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Thursday 24 October** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Frequency of dexamethasone injections

Description of problem	Description of proposed amendment	Justification for amendment
P100 of the ERG report states: *"The assumption of 4 doses of dexamethasone during the first year is stated as being drawn from the STA of ranibizumab for RVO (TA283). Table B62 of the Novartis submission for the STA of ranibizumab for RVO suggests only 2 doses of dexamethasone during the first year, a total of 8 visits being required so resulting in 6 dedicated monitoring visits."* The Novartis STA submission is not the most recent reference. The initial model was superseded during the appraisal process.	The report should reference the most recent Novartis model which was used for decision making in TA283. The model was changed during the appraisal process. Section 3.35 of the FAD of TA283 states: *"…In addition, the manufacturer considered that the dexamethasone re-treatment frequency included in the original model (every 6 months) was conservative and therefore applied a re-treatment frequency of 4 months to the revised model."*	This should be amended for correct referencing of TA283 and consistency of approach. Our estimation of 4 doses in the first year is based on retreatment every 4 months (with the first injection in administered in week 0 and repeated at week 16, 32 and 48).

Issue 2 Effectiveness assumptions and frequency of dexamethasone injections

Description of problem	Description of proposed amendment	Justification for amendment
P101 states: *"In the light of this either 2.00 doses or 1.86 doses of dexamethasone during the first year seems more reasonable. The 1.86 doses from the pooled GENEVA data for the CRVO is aligned with the clinical effectiveness data, and so seems to be the most reasonable to use for the base case."* This is not the case as clinical effectiveness data from GENEVA was not used in our model in weeks 24-52, as indirect comparisons were not possible.	It should be clarified that an assumption of maintained benefit was assumed for dexamethasone in weeks 24-52. This was conservative considering that the same assumption was made for aflibercept which was significantly more effective than dexamethasone in the indirect comparison up to week 24. To maintain benefit, an assumption of treatment every 4 months is more appropriate as the ERG conclusions in Section 3.42 of the FAD for TA283 indicate this link between stability and more frequent dexamethasone injections. Moreover, this is additionally conservative given we have not increased adverse event rates, as would be expected from more frequent injections, as also stated in section 3.42 of the FAD.	Consistency of approach with TA283 (section 3.35 and 3.42) and more appropriate fit of clinical effectiveness assumption in the first year with number of dexamethasone injections.

Issue 3 Inclusion of ischaemia patients

Description of problem	Description of proposed amendment	Justification for amendment
P51: Although our submission presented data to show the benefit of aflibercept in perfused and non-perfused subgroups in the pivotal trials, the ERG indicates it would have been useful if more detail on ischaemic state had been given such as median or mean areas of non-perfusion.	It would be suitable to clarify that data on median or mean areas of non-perfusion is not available and, therefore, cannot be provided. In addition, it should be noted that the severity of ischaemia does not affect management of CRVO and, therefore, classification of ischaemia into ranges (mild, moderate, severe) is not standard clinical practice.	Such an amendment will add clarity to the issue. There exist other definitions of ischaemia apart from Hayreh. For example, the hallmark Central Vein Occlusion Study Baseline and Natural History Report (Arch Ophthalmol. 1993;111:1087-1095) used the 10 disc area to differentiate non-perfusion.

Issue 4 Calculation of utility values

Description of problem	Description of proposed amendment	Justification for amendment
P87: The ERG indicates that base case utility values in our manufacturer submission were derived based on the treated eye (Section 5.2.7). This is not the case.	It would be appropriate to report that the utility values were analysed based on the WSE of the patients and it was assigned based on the lowest BCVA score achieved in either eye.	We have been clear about this in our manufacturer submission, section 7.4.9: *"EQ-5D scores collected at each time point in the GALILEO clinical trial were mapped to a utility index using an established algorithm (see Section 7.4.4). The utility values derived from these scores were then analysed based on the WSE of the patients, to reflect that patients enrolled in the aflibercept CRVO trials were predominantly tested in their WSE."*

Issue 5 Validation of results with dexamethasone

Description of problem	Description of proposed amendment	Justification for amendment
P99: The ERG indicates a mismatch	It would be correct to state that the results of the	Such an amendment will add clarity.

between the model results and those written in the submission for the scenario with dexamethasone.	dexamethasone scenario should include adverse events given the different safety profiles of anti-VEGF and steroids.	

Issue 6 Reference to stopping rules

Description of problem	Description of proposed amendment	Justification for amendment
P78: *"Stopping rules.* *The ERG think there may be case for having some stopping rules, which might include;* *- deterioration in VA after three injections* *- no fall in oedema fluid or CRT. The current re-treatment criterion mentions a 50 µm rise in CRT, but this implies that it had fallen previously."*	It would be appropriate to note that stopping rules should be in line with the marketing authorisation for aflibercept for macular oedema secondary to CRVO. The current SmPC for aflibercept for CRVO states that, *"if there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended."* This is similar to the current SmPC for ranibizumab for macular oedema secondary to RVO which states that, *"if there is no improvement in visual acuity over the course of the first three injections, continued treatment is not recommended"*.	No additional stopping rules were recommended for ranibizumab in TA283. While it would be possible to estimate the proportion of patients benefitting at 3 months from the aflibercept trial data, it would not be possible to estimate a similar parameter for the comparators. Therefore, any further analysis would be heavily based upon assumptions rather than evidence.

Issue 7 Reference sources

Description of problem	Description of proposed amendment	Justification for amendment
P101-102: The ERG was unable to source the following: *A) "The ERG has not been able to source the 0.50% rate of retinal tears within the submission, the text on page 112 of the submission noting "retinal haemorrhage and retinal tear (COPERNICUS: [redacted])"".*	The addition of the following clarifications would be beneficial: A) In the pooled 6m CSR, Table 1.3.1 / 14 shows that there were [redacted] incidences of retinal tears (sham: [redacted] Eylea[redacted]) across the two trials. (Pooled 6m COPERNICUS and GALILEO CSR, Table 1.3.1 / 14: Number of subjects with ocular treatment-emergent adverse events of the study eye by primary system organ class and preferred	Such an amendment will add clarity and enable sourcing of references for transparency purposes.

	term (Safety Analysis Set)). Therefore the sentence in the submission on page 112 should refer to 2 events of retinal tear across the two arms (not “sham” – this was a typo) for the pooled GALILEO and COPERNICUS trials. It does not impact the analysis.	
B) *“Subsequent to the end of treatment a 4 weekly probability of worsening by one health state of 0.0296% is applied. The submission states that this is based upon 7.4% worsening by at least 15 letters over 20 years, as drawn from the Beaver Dam study as reported in Klein et al (1991).[...]The text supplied in the manufacturer reference pack for Klein et al (1991) does not report the values used within the submission. The 0.296% rate of worsening by 15 letters each 4 week cycle may be a lower bound. Consequently, sensitivity analyses increasing this rate are desirable.”*	B) The manufacturer used the same approach as Novartis (see page 194, manufacturer submission), i.e. it was based on the 7.4% estimate derived from Klein 1991 (Table 3) as follows: The BCVA increase from “no impairment” (ability to read 41-70 letters) and “mild impairment” (26-40 letters) corresponds to a difference of 15-30 letters i.e. 3-6 lines. It was assumed that 7.4% of the patients experience a loss of 3-6 lines over 20 years. This 7.4% estimate was derived by subtracting 2% (age group 43-54) from 9.4% (age group 65-74). Since there was no observational data showing the decline in BCVA in the same patient population over 20 years, BCVA was compared in two age groups (43-54 and 65-74) that have a difference of 20 years. The age groups of 43-54 and 65-74 were preferred to older groups of 55-64 and 75+, which would be closer to the mean patient age of patients treated for CRVO (64 years old), because there was no information about the upper boundary of the 75+ age group. Conversion of the 7.4% rate into a 0.0296% probability can be found on model Tab “Data_Inputs_UK”, cells Q36-Q37.	Such an amendment will add clarity and enable sourcing of references for transparency purposes.
C) *“The ERG cannot source the proportion with raised IOP from Brown et al, but table B48 of the economics section of the Novartis submission for the STA of ranibizumab for RVO gives a pooled value for the BRAVO and CRUISE trial of 10%.*	C) The percentage of patients with raised IOP was taken directly from table B48 of the Novartis submission as indicated in the Bayer manufacturer submission. The source indicated in the Bayer model (Brown 2010) is incorrect. The percentage of patients with raised IOP, of 10%, was	Such an amendment will add clarity and enable sourcing of references for transparency purposes.

This rate may relate to 12 months, suggesting the 5.0% that is applied for the first 6 months in the manufacturer base case."	adjusted to 6 months (i.e. 5%) based on the assumption that half of the events occur at the first 6 months.	
D) *"The ERG could not directly source the 0.0003 four week disutility for raised IOP from Vaahtoranten-Lehtonen et al (2007)". This is unclear in the paper. The manufacturer has multiplied the 0.01 by 0.03 to arrive at the 0.0003 QALY impact. The intention appears to be to divide it by 365 to yield one day's duration of disutility, which would require multiplication by approximately 0.003. This is then further divided by 13 within the model structure."*	D) The value of 0.01 of disutility mentioned in table B55 of the Novartis submission and based on the paper by Vaahtoranten-Lehtonen was used to inform the IOP increased disutility in the aflibercept model as well. From table B55 of the Novartis submission, it can be inferred that: •this paper estimated a per month disutility of 0.01 for patients experiencing increased IOP and •the duration of the disutility associated with IOP treated with drugs (as opposed to surgery) is assumed to be one day per month, i.e. 1/30=0.03 (in months). Given that the majority of the IOP patients are treated for IOP using drugs in the aflibercept model, it was assumed that the 0.01 disutility should be adjusted so that it is applied for 1 day. Therefore, 0.01 has been multiplied by the duration that the disutility lasts, 0.03 i.e. 0.01*0.03 =0.0003.	Such an amendment will add clarity and enable sourcing of references for transparency purposes.

Issue 8 Reference sources

Description of problem	Description of proposed amendment	Justification for amendment
P104: The ERG asks for clarification on the dates of the data cuts for observed values and LOCF data.	It may be noted that observed data used for transition probabilities (TPs) in the original model was from April 2012. The ERG noted some inconsistencies in this data. As a result, data from a more recent data cut at July 2013 was used at clarification when it was realised that the observed data from April 2012 contained inconsistencies. Moreover, to be completely consistent with the results reported from the pivotal clinical studies in the clinical effectiveness section, LOCF data	The change to more recent LOCF data from July 2013 as a source of TPs has a small impact on the ICERs in favour of aflibercept. The base case versus ranibizumab changes from £[redacted] to £[redacted] and versus dexamethasone changes from £[redacted] to £[redacted].

	was then used, as in the primary clinical analysis.	

Issue 9 Reference to an unpublished NMA undertaken by an academic group (Ford *et al.* submitted for publication)

Description of problem	Description of proposed amendment	Justification for amendment
P13 (also discussed on page 66. 67, 76 and 77). *"The ERG had access to a NMA undertaken by an academic group (Ford et al submitted for publication)…"* It is not possible to check the factual accuracy of this information and any subsequent conclusions given the limited information provided.	Full details of the systematic review and network meta-analysis by Ford et al. should be made available in the appendix for scrutiny of methodology, along with discussion of strengths and limitations of the analysis (including heterogeneity).	This is required for transparency of any decision making based on this evidence. For example, it is unclear whether any consideration of study quality, heterogeneity and safety has been made in order to derive subsequent conclusions on potential cost effectiveness of the included treatments.

Issue 10 Availability of final SmPC

Description of problem	Description of proposed amendment	Justification for amendment
P25: The report states that the SmPC is no available	The SmPC was made available on the EMA website at the time of marketing authorisation (following submission).	Such an amendment will add clarity.

Issue 11 Confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment
P78 Confidentiality marking	A revised highlighted and redacted submission was provided to NICE on 18th October. This document should be used as a reference for the CiC marking in the ERG report.	Maintain confidentiality of patient access scheme.