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11th March, 2015

Dear Meindert,

NICE Single Technology Appraisal (STA). Dexamethasone intravitreal implant for treating diabetic macular oedema [ID653] - Appraisal consultation document (ACD).

Thank you for the opportunity to provide comments on the above appraisal where Novartis are a registered commentator.

Novartis welcomes the decision by NICE to approve a treatment option for those patients with diabetic macular oedema only if:

- The implant is to be used in an eye with an intraocular (pseudophakic) lens **and**
- Their diabetic macular oedema does not respond to non-corticosteroid treatment or such treatment is unsuitable for them.

The following document answers the following questions as requested by NICE – the responses for question two are provided in the order in which they are written within the ACD:

1. Has all of the relevant evidence been taken into account?
2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Yours sincerely,

[redacted]

[redacted] [redacted]

1. Has all of the relevant evidence been taken into account?

Systematic Review & Network Meta-analysis

Novartis conducted a systematic review and network meta-analysis in DMO relevant to the NICE decision problem in Q1 2014. The outputs of this work were published on July 16th in PLOSone journal[1].

The manufacturer appears not to have considered all the appropriate and relevant evidence within their network meta-analysis. Of significance and impacting the effect size of ranibizumab was the omission of other key evidence (central to the decision problem). Table 1 below highlights the evidence that was omitted from the manufacturer's network meta-analysis.

Table 1. Key evidence omitted from the manufacturer's network meta-analysis and relevant to the decision problem.

Treatment Node	Omitted Evidence
Ranibizumab	READ-2 [2] RESOLVE[3]

In addition to the omissions as described above, the manufacturer has chosen to *include* the REVEAL study[4] as part of the network to inform the relative effectiveness estimate of ranibizumab. This study evaluated ranibizumab in an *exclusively* Asian population and is thus not representative of the UK wider population. Consequently, it should not be included within this evidence network for reasons of heterogeneity of inclusion criteria compared to the other studies.

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Page 10, Section 3.20.

The ACD document incorrectly describes the PROTOCOL **1** study – the study is called the PROTOCOL **I** study (i.e. the letter "I" not the number "1").

Pages 15-16, Section 3.32.

In terms of the model structure, Novartis notes that the manufacturer uses two very wide Markov states at the high and low ends of visual acuity (compared to 10 letter states in the rest of the structure). Specifically the use of "76 letters or more" AND "35 letters or less" rather than splitting the states into:

High visual acuity: 2 states – one for "76-85 letters" and another for "86-100 letters."

Low visual acuity: 2 states – one for “26-35 letters” and another for “≤25 letters.”

The net effect of the manufacturer’s model structure is reduced granularity and QALY underestimation – i.e. the ability to be able to calculate incremental differences in utility between treatments.

The various models of utility that have been applied to technology appraisals in this field have linear functions (please see Table 2) and thus utility differences that occurred are *lost* when using this homogenised upper and lower state structure. This approach favours less effective treatments as is the case within the present context and might have led to overly optimistic ICERs for dexamethasone.

Furthermore, the manufacturer’s invalid assumption that a patient may only transition by a maximum of 1 state in a cycle further exacerbates the problem of QALY underestimation.

Table 2. Utility by visual acuity.

Czoski-Murray[5]. Utility by visual acuity in the better seeing eye.

Visual Acuity	Utility in Better Seeing Eye
VA 86-100 letters	**0.850**
VA 76-85 letters	**0.758**
VA 66-75 letters	0.685
VA 56-65 letters	0.611
VA 46-55 letters	0.537
VA 36-45 letters	0.464
VA 26-35 letters	**0.390**
VA<25 letters	**0.353**

Brown et al. (1999)[6]. Utility by visual acuity in the better seeing eye.

VA 86-100 letters	**0.920**
VA 76-85 letters	**0.880**
VA 66-75 letters	0.770
VA 56-65 letters	0.755
VA 46-55 letters	0.670
VA 36-45 letters	0.665
VA 26-35 letters	**0.645**
VA<25 letters	**0.510**

Pages 18-19, Section 3.39.

Novartis also notes that the manufacturer does not undertake sensitivity analyses with the utility algorithms that have already been applied within the context of recent NICE decision making (in TA274[10]) and the ongoing appraisal for aflibercept in DMO. Instead the manufacturer undertakes a sensitivity analysis with EQ-5D, which is known to be insensitive to vision related diseases[7, 8]. Novartis feels that it is appropriate to ensure that the methodology associated with NICE decision making is harmonised between appraisals where possible.

The utility algorithms selected by the manufacturer for the present submission favour less effective treatments since the delta between the highest and lowest vision states is significantly smaller: 0.16 was the maximum delta presented at the committee meeting for the manufacturer's choice of utility data compared to 0.50 for Czoski-Murray[5] and 0.41 for Brown (1999)[6]. As a consequence, the economic modelling is underestimating the ICERs for the dexamethasone comparisons.

It is also worth noting the perverse irony in the choice of utility algorithm employed by the manufacturer for their base case - Visual Function Questionnaire Utility Index (VFQ UI), calculated directly from the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) collected in the MEAD clinical trials. The results demonstrate that dexamethasone **is no more effective than sham** at improving health related quality of life (defined by NEI VFQ-25) on both the composite score and individual items as reported on page 7 of the ACD and discussed at the committee meeting:

> "3.11. There were no statistically significant differences in the mean average change in health-related quality of life when comparing dexamethasone intravitreal implant with sham procedure in the MEAD trials (overall composite score: dexamethasone 1.9 versus sham 2.2, p=0.64; general vision: dexamethasone 4.5 versus sham 5.0, p=0.92; difficulty with near vision: dexamethasone 5.8 versus sham 4.3, p=0.25; difficulty with distance vision: dexamethasone 2.9 versus sham 2.7, p=0.70; mental health symptoms due to vision: dexamethasone 4.6 versus sham 4.8, p=0.89)."

Page 20, Section 3.41.

> "For ranibizumab, the total cost was £858.85 for unilateral disease and £1659.36 for bilateral disease"

Novartis requests that the additional words "without PAS" are added to the sentence for clarity.

Page 20, Section 3.43.

The assumptions employed by the manufacturer for the number of monitoring visits with ranibizumab (based on the summary of product characteristics and TA237) are out of date since the ranibizumab SmPC has changed and does not require monthly monitoring:

Please see precise wording from Section 4.2 of the ranibizumab SmPC[9]:

> "…monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.
>
> Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography)."

Page 21, Section 3.44.

The ACD document incorrectly describes the PROTOCOL **1** study – the study is called the PROTOCOL **I** study (i.e. the letter "I" not the number "1").

Page 22, Section 3.46.

> "In people with a pseudophakic lens, treatment with ranibizumab resulted in a deterministic incremental cost-effectiveness ratio (ICER) of £50,905 per QALY gained…"

Please could the additional words, and "not stratified by retinal thickness of >400 micrometres" be added to make it clear that this ICER is for the full pseduophakic DMO population.

Page 31, Section 3.73.

> "The restriction of transitions between health states for each cycle, so that each patient could only move 1 BCVA health state per cycle"

Novartis agree with the ERG that this assumption is not valid.

It is important to recognise the collective effects of several of the manufacturer's key modelling assumptions (model structure, utility source, and the state transition restrictions as here) all leading to reduced granularity and favouring dexamethasone.

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Novartis agrees that the provisional recommendations are sound and a suitable basis for guidance to the NHS.

References:

1. Regnier S et al. Efficacy of Anti-VEGF and Laser Photocoagulation in the Treatment of Visual Impairment due to Diabetic Macular Edema: A Systematic Review and Network Meta-Analysis. PLOS one, July 2014, volume 9, issue 7.

2. Nguyen QD et al. Primary end point (six months) results of the Ranibizumab for Edema of the mAcula in diabetes (READ-2) study. Ophthalmology 116: 2175–2181 e2171, 2009.

3. Massin P et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. Diabetes Care 33: 2399–2405, 2010.

4. Ohji M, Ishibashi T, REVEAL study group. Efficacy and safety of ranibizumab 0.5 mg as monotherapy or adjunctive to laser versus laser monotherapy in Asian patients with visual impairment due to diabetic macular edema: 12-month results of the REVEAL Study. ARVO Meeting Abstracts 2012; 53(6):4664.

5. Czoski-Murray C, Carlton J, Brazier J et al. Valuing condition-specific health states using simulation contact lenses. Value Health 2009; 12:793-9.

6. Brown GC. Vision and quality-of-life. 1999; 97: Trans Am Ophthalmol Soc 1999; 97:473-511.

7. Soubrane G, Cruess A, Lotery A, et al. Burden and health care resource utilization in neovascular age-related macular degeneration: Findings of a multicountry study. Archives of Ophthalmology 2007; 125:1249-1254.

8. Lloyd A, Nafees B, Gavriel S et al. Health utility values associated with diabetic retinopathy. Diabet Med 2008; 25:618-24.

9. Electronic Medicines Compendium. Ranibizumab summary of product characteristics. https://www.medicines.org.uk/emc/medicine/19409 accessed 26th Feb, 2015

10. NICE (2013). Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237). http://www.nice.org.uk/guidance/ta274/resources/guidance-ranibizumab-for-treating-diabetic-macular-oedema-rapid-review-of-technology-appraisal-guidance-237-pdf accessed 26th Feb, 2015.