

**Comments from Novartis Pharmaceuticals UK Limited on the Appraisal Consultation Document (ACD) for the Health Technology Appraisal of Ranibizumab for the Treatment of Wet AMD**

Thank you for your invitation to comment on the above referenced Appraisal Consultation Document (ACD) and accompanying documents, which were released on the 7<sup>th</sup> June 2007. Whilst Novartis are pleased that patients with predominantly classic lesions will be allowed access to ranibizumab treatment, the decision to deny ranibizumab to patients with minimally classic and occult lesions is not consistent with the available evidence base, nor does it take into account the degree of unmet clinical need in these patients. In addition, the restriction which limits treatment to the better seeing eye for predominantly classic lesions, cannot be justified on scientific, moral or ethical grounds. We believe, therefore, that the ACD is perverse in the light of the evidence submitted and that, accordingly, the preliminary recommendations therein do not constitute a reasonable or scientifically sound basis on which to develop guidance to the NHS.

We do not believe that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.

We do not believe that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate.

We do not consider that all of the relevant evidence has been taken into account.

Novartis' main concerns regarding the preliminary recommendations, are summarised below:-

- 1. The decision not to recommend ranibizumab for patients with minimally classic and occult lesions relies on an estimate of cost-effectiveness which is based on 24 injections over the course of 2 years, day case procedure costs and an underestimate of the costs of blindness. The combination of these factors has resulted in an incremental cost-effectiveness ratio (ICER) which grossly underestimates the cost-effectiveness of ranibizumab.**
- 2. The recommendation that ranibizumab treatment should be limited to the better seeing eye is not supported by the available evidence base.**
- 3. The implication that the recommended posology for ranibizumab may result in a reduction in benefits compared to those observed in the MARINA and ANCHOR studies is inaccurate and misleading.**

However, in order to demonstrate our continued commitment to patients, and Novartis' desire to collaborate with the Institute to facilitate broader patient access to innovative and valuable treatments, Novartis is willing to consider capping the dose of ranibizumab. This concept was discussed, in principle with Dr Carole Longson on 9<sup>th</sup> July 2007 and the Department of Health, NICE liaison team, on 11<sup>th</sup> July 2007. As agreed, after further discussion with the Department of Health and NICE, further details of the scheme will be provided prior to the Appraisal Committee meeting on the 9<sup>th</sup> August 2007.

These issues, as well as our other comments, are addressed in more detail below and are set out as per the requested headings.

**A. We do not believe that the provisional recommendations as detailed in the ACD are justified nor do they constitute a reliable basis for the provision of sound guidance to the NHS.**

**A1. The decision not to recommend ranibizumab for patients with minimally classic and occult lesions relies on an estimate of cost-effectiveness which is based on 24 injections over the course of 2 years, day case procedure costs and an underestimate of the costs of blindness. The combination of these factors has resulted in an incremental cost-effectiveness ratio (ICER) which grossly underestimates the cost-effectiveness of ranibizumab.**

Reduced dosing frequency vs monthly injections.

The SHTAC model assumes that 24 injections are administered over the course of 2 years. This is inconsistent with the posology recommended by the EMEA, which represents a pragmatic and clinically directed approach to dosing. Therefore, the estimates from the Assessment Group's model grossly underestimate the cost-effectiveness of ranibizumab. In routine practice, and as acknowledged by clinical specialists in the ACD, most patients will receive considerably less than 24 injections. Two year results from the published PrONTO study using ranibizumab, demonstrate a mean improvement in visual acuity of 10.7 letters, and an improvement in visual acuity by  $\geq 15$  letters in 43% of patients. These results are similar to those observed in the MARINA and ANCHOR studies and were achieved with an average dose of 9.9 injections over 24 months. Although, this is a relatively small, open label study, the pragmatic dosing regimen used in the study and its results strongly support the view that in routine clinical practice, a dosing strategy based on clinical need will significantly reduce the number of injections administered without compromising the level of benefits achieved. Following receipt of the ACD, Novartis conducted a survey involving 47 ophthalmologists who have considerable experience with ranibizumab. So far 19/47 ophthalmologists have responded. Results from this survey suggest that 58% patients will receive between 3 and 6 injections over 12 months and 38% will receive more than 6 injections but less than 12 injections. This is consistent with the drug and disease model submitted by

Novartis on the 1<sup>st</sup> August 2006, which suggests that on average 8 injections are likely to be required in the first year and 6 injections in the second year.

The PIER trial demonstrated that an initial loading dose of monthly injections of ranibizumab for 3 months, followed by fixed quarterly injections, is superior to sham treatment for the primary endpoint and a number of secondary outcomes. In terms of the primary endpoint, the mean change in visual acuity from baseline, the difference between ranibizumab and sham injection observed in the PIER trial is similar (16.1 letters) to results from the MARINA and ANCHOR trials (17.7 to 20.8 letters). In addition, an initial improvement in mean visual acuity was seen at month 3, which is consistent with the findings from the MARINA and ANCHOR studies. In the PIER study 49% patients, compared to 70% and 75% MARINA and ANCHOR respectively lost fewer than 5 letters (1 line) visual acuity between baseline and 12 months. This suggests that the fixed, quarterly, dosing regimen employed in the maintenance phase of PIER was adequate for a large proportion of patients to achieve the results observed in the MARINA and ANCHOR trials. It also suggests that some patients are over-treated using the monthly dosing regimen. In order to address this, the licensed dosing recommendations have been adopted to tailor the dose according to clinical need, rather than a fixed dosing interval regardless of response.

Section 4.3.10 of the Appraisal Consultation Document (ACD) states,

*“The Committee was mindful of the results of the PIER study showing that the reduced frequency regimen was associated with reduced benefits.”*

This erroneously implies that a reduced dosing regimen will result in reduced benefit. The key distinction is that PIER is based on treating all patients in a fixed dosing manner, irrespective of patient response, where as the recommended UK posology for ranibizumab is a flexible approach and means that re-treatments, following the loading phase, are dictated by patient response to therapy. In practice, this means that the dose of ranibizumab will be individualised to achieve maximum benefit with minimum dosing. As well as being pragmatic, this dosing strategy represents a more effective and efficient strategy than the fixed dosing regimen employed in the PIER study.

Results from the published, PrONTO trial demonstrate that an “as required” dosing strategy can achieve benefits comparable to those achieved in the MARINA and ANCHOR trials with an average of 9.9 injections over the course of 2 years.

In summary, the recommended posology for ranibizumab represents a pragmatic, effective and efficient dosing strategy for the treatment of wet AMD, which is likely to result in a level of benefits similar to those observed in the MARINA and ANCHOR studies.

#### Day case procedure costs vs. outpatient visits.

As set out in “The Royal College of Ophthalmologists Intravitreal Injections Procedure Guideline”<sup>i</sup>, intravitreal injections may be carried out either as an outpatient procedure or as a day case procedure. In practice, there is likely to be variation in the setting used, however, the assumption, used in the SHTAC model, that the cost of administering treatment will be broadly in line with the cost of a day case procedure, is an overestimate as it represents the upper extreme rather than a realistic treatment scenario.

#### Cost of Blindness.

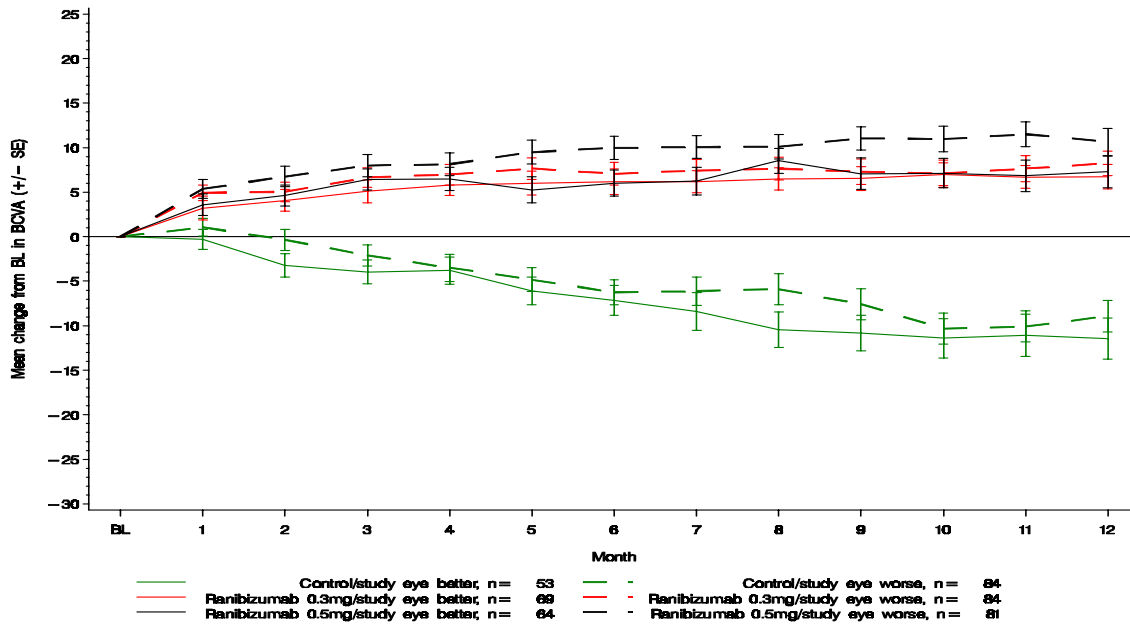
Section 4.3.13 of the ACD acknowledges the fact that clinical specialists consider the costs of blindness used in the Assessment Group’s model to be too low. This effectively means that cost effectiveness of treatment will also be underestimated. The Appraisal Committee argue that this is balanced by the “*overestimation of the QALY gain*”. However, this is neither a fair nor reasonable evaluation as the “*overestimation of QALY gain*” is purely speculative, whilst the underestimation in the costs of blindness can be quantified and is verified by clinical experts.

### **A2. The recommendation that ranibizumab treatment should be limited to the better seeing eye is not supported by the available evidence base.**

Section 1.1 of the ACD states that ranibizumab treatment should only be reserved for the better seeing eye. The available evidence does not support this view and it is not clear from the ACD what evidence has been used to support this decision. In practice, this will mean that patients will be allowed to go blind in one eye before being eligible for treatment, which is morally and ethically unacceptable.

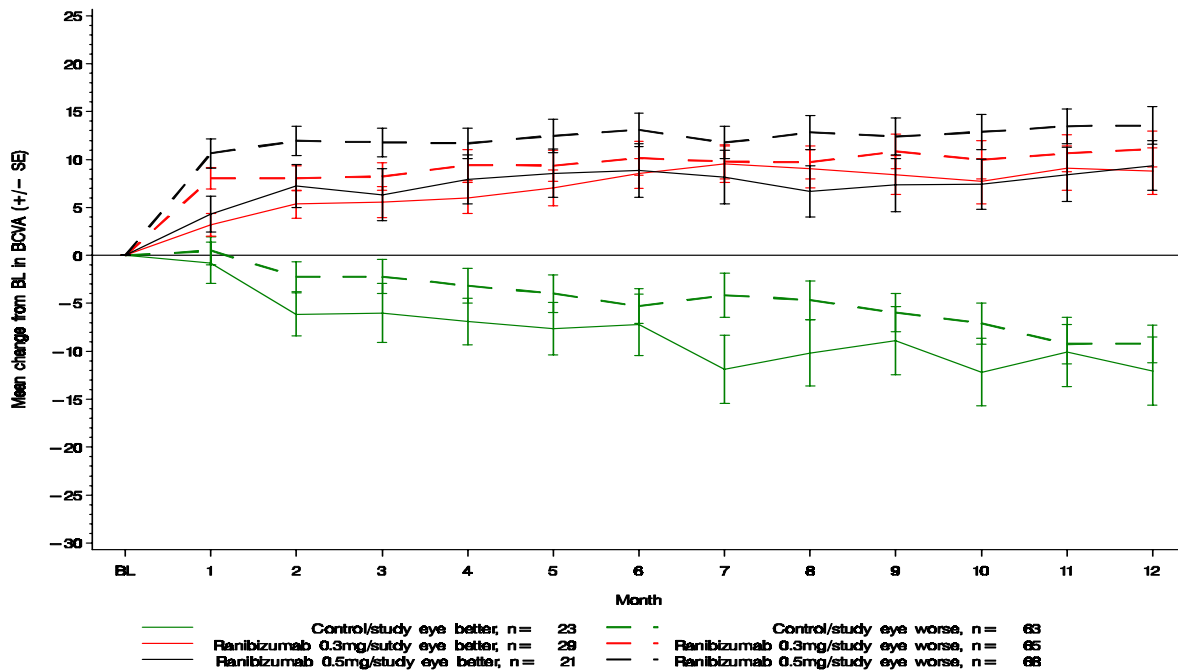
Patient reported outcomes from MARINA and ANCHOR demonstrate statistically significant and clinically meaningful improvements in near activities, distance activities, and vision-specific subscales of the VFQ-25 instrument. These benefits were demonstrated regardless of whether patients received ranibizumab in the better- or worse seeing eye.<sup>ii</sup> In addition, results from the ANCHOR, MARINA and PIER trials all demonstrate that, in patients who received ranibizumab in the first or worst seeing eye, experienced improvements in visual acuity at 12 months of the same order of magnitude as results observed in the second or better seeing eye. These results are summarised in the following graphs.

Study eye better/worse visual acuity than fellow eye: Mean change from BL in BCVA over time by treatment groups  
For difference between best and worst eye of at least 14 letters



/vob/CRFB002/pool/pool\_001/report/pgm\_eff/dm\_fmva\_bw\_diff.sas - 29JUN2007:18:53

Study eye better/worse visual acuity than fellow eye: Mean change from BL in BCVA over time by treatment groups  
For difference between best and worst eye of at least 14 letters



/vob/CRFB002/pool/pool\_001/report/pgm\_eff/dm\_fava\_bw\_diff.sas - 29JUN2007:19:09

A study by Williams et al, which assessed the psychological impact of macular degeneration in older persons who were legally blind in one or both eyes, found that psychological distress in both groups was significantly worse than that in non-affected older people.<sup>iii</sup> The level of psychological distress was comparable to reports from patients with melanoma, acquired immunodeficiency syndrome and bone marrow transplant. Participants who were legally blind in one or both eyes were limited in their ability to carry out basic daily activities. In the study, patients who were legally blind in only one eye recorded higher scores (more severe distress) in almost all areas than patients who were blind in both eyes. The authors also found that for older persons with advanced AMD, greater emotional distress was then reflected in worse quality of life and more difficulty in carrying out daily activities. This study, therefore, confirms that the presence of a single affected eye exerts substantial adverse effects on functional ability and quality of life comparable to those experienced with bilateral visual impairment.

Brown et al compared quality of life associated with monocular and binocular vision using a time trade off method.<sup>iv</sup> The authors concluded that patient preference based quality of life was better in patients with eye disorders who had good bilateral visual acuity, than in those with only good unilateral visual acuity.

In summary, the preliminary recommendations do not take into account the relative benefits of binocular and monocular vision, or the distress caused by an untreated affected eye. There, to our knowledge, is no evidence to support the restriction of treatment to the better seeing eye. Conversely, the available evidence suggests that there are significant improvements in patient reported outcomes, regardless of whether treatment was administered to the better or worse seeing eye. In addition, a vast majority (88%) of the ophthalmologists responding to our survey are of the view that it would be unethical to restrict treatment to the better seeing eye.

**B. The current recommendations do not take into account all of the available evidence. In addition, the summaries of clinical and cost effectiveness are not reasonable interpretations of the available evidence base.**

**B1. The implication that the recommended posology for ranibizumab may result in a reduction in benefits compared to those observed in the MARINA and ANCHOR studies is inaccurate and misleading.**

No other therapies are currently available on the NHS to treat patients with minimally classic and occult lesions associated with wet AMD. This means

that patients will be denied access to a clinically and cost effective treatment, which could prevent progression to blindness with its devastating consequences for patients and their families and/or carers.

The results from the MARINA and ANCHOR trials demonstrate that ranibizumab is effective regardless of lesion type or size. These results are summarised in the following table.

**Summary of Results from MARINA and ANCHOR Trials**

	<b>Minimally classic and occult lesions (MARINA)</b>	<b>Predominantly classic lesions (ANCHOR)</b>
Loss of <15 letters (3 lines) on the EDTRS chart at 12 months	95%	94.3%
Difference in mean change from baseline visual acuity	17 letters (p=0.0001)	20.7 letters (p=0.0001)
Proportion of subjects gaining at least 15 letters visual acuity	33.8% ranibizumab vs. 4.6% control	40.3% ranibizumab vs. 5.6% control

There is no other available therapy that has shown these benefits in randomised controlled clinical trials of either stabilisation or improvement in vision in 95% and 34%-40% respectively.

**B2. The combined impact of a number of conservative assumptions significantly underestimates the cost-effectiveness of ranibizumab treatment.**

The decision not to endorse ranibizumab treatment for minimally classic and occult lesions relies on an estimate of cost-effectiveness, which is based on a number of conservative assumptions. These assumptions represent an excessive number of treatments (Ref. A1 above), overestimated administration costs (see A1 above), and underestimated costs of blindness.

In summary, if more realistic assumptions were adopted, the ICERs relating to ranibizumab for the treatment of minimally classic and occult lesions would be reduced to a level deemed to be acceptable according to the conventionally accepted threshold.

**Other comments**

### **Section 3.3, page 6**

It should be noted that the risk of endophthalmitis with ranibizumab is low at a rate of 0.07% per injection. This should be specified in order to provide a comparison with pegaptinib which is stated in the ACD to have a 0.1% risk of endophthalmitis per injection.

### **Section 4.3.5, page 19**

This section of the ACD states: *“However, the Committee considered a point raised by consultees that preliminary results of an ongoing study suggests that ranibizumab may be associated with an increased risk of stroke and agreed that although this was an important issue it was inappropriate to draw conclusions at this stage.”*

The report, suggesting a possible increased risk of stroke, was taken from the interim results of the SAILOR study based on an interim analysis comprising 77% of one of two cohorts. A statistically lower incidence of stroke was observed in patients on Lucentis 0.3 mg compared to patients on 0.5 mg (0.3% and 1.2%, respectively [ $p = 0.02$ ]). Overall, the rate of stroke observed with Lucentis 0.5mg was consistent with data from the MARINA and ANCHOR trials (Brown et al, 2006; Rosenfeld et al, 2006). Furthermore, the rate of stroke observed with ranibizumab 0.5mg was no higher than the rate of stroke in the general population of a similar age and profile (Wong et al, 2006; Goehring et al, 2006). Patients with a history of prior stroke appeared to be at a higher risk of subsequent stroke. It is important to note that, although the rate of stroke in the 0.3 mg treated patients was statistically lower, this dose of Lucentis is not thought to be protective of stroke.

A subsequent and more recent interim analysis of the SAILOR data (performed on more patients from cohort 1) showed that the rates of stroke between patients on the 2 ranibizumab doses were 0.6% (3mg) and 1.2% (0.5mg), no longer a statistically significant difference.

These data have been shared with the US Food and Drug Administration (FDA), and the UK Medicines and Healthcare products Regulatory Agency (MHRA). Both the FDA and the MHRA have agreed that no changes to the prescribing information are required as the incidence of stroke in the patients on ranibizumab 0.5mg was similar to that in the general population.

### **Section 4.3.10, page 21**

This section of the ACD suggests that acceptance of the SHTAC base case scenario incorporating the cost of 24 injections is based on the fact that treatment may extend beyond 2 years. However, it should be noted that if costs are to be considered beyond 2 years then likely benefits beyond 2 years should also be taken into account and modelled appropriately as maintenance of the improved vision maintained in years 1 & 2.



#### **Section 4.3.12, page 21**

This section of the ACD suggests that utilities derived using the EQ-5D “*might*” result in a much smaller difference however, there is no evidence to support this view.

The Assessment Group’s economic model is based on a published study using VFQ 25 which is a validated assessment tool for patients with visual problems and which employed methods consistent with the NICE reference case. Similarly the Novartis model uses utility values derived from a study which used contact lenses in the general population to simulate different visual acuity states. The utilities were elicited using a preference based technique consistent with the NICE reference case.

In summary, the utility values adopted in the economic models are based on the best available evidence and are, therefore, the most appropriate for decision-making purposes. Furthermore, it should be noted that the utilities used in the models are based on visual acuity only. No account has been taken of other aspects of vision, such as contrast sensitivity, which are also likely to have an impact on health related quality of life. Consequently, QALY gain may be underestimated.

#### **Section 6.1, page 25**

It should be noted that the research recommendations suggested in bullets 3 and 4 of this section are already being evaluated in ongoing Novartis sponsored studies.

The SUSTAIN study is a 12-month open-label, multicentre, phase IIIb study assessing safety and efficacy of ranibizumab in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration. Ranibizumab is administered in line with the UK licence, in that after the initial loading phase of 3 consecutive monthly intravitreal injections, further re-treatment is based on BCVA or OCT changes. Recruitment commenced in Q3 2006 and a total of 600 patients worldwide are targeted. UK recruitment targets were achieved in March 2007. This data will confirm the data seen in PrONTO, and also within clinical practice in the UK (as evidenced by the Retinal Survey)

The SUMMIT Mont-Blanc study is a 12-month randomised, double-masked, controlled, multicentre, phase II study assessing safety and efficacy of verteporfin PDT administered in conjunction with ranibizumab, versus ranibizumab monotherapy, in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration. All therapies in this study will be given on an “as required basis”, after the initial loading treatment (1 course of PDT and 3 injections of ranibizumab). Recruitment for this study has now started.

#### **Section 6.1, page 25**

This section states that further research should include an evaluation of the cost-effectiveness of bevacizumab. However, it should be noted that the bevacizumab

evidence base lacks any formal clinical trial data in patients with wet AMD. This means that the safety and efficacy of bevacizumab for ocular treatment has not been demonstrated.

In addition, the draft protocol outlining the planned head to head (IVAN) study comparing ranibizumab and bevacizumab, currently advocates a dosing strategy for ranibizumab which is not consistent with the recommended dosing regimen as detailed in the Summary of Product Characteristics (SmPC).

In summary, the ACD is perverse in light of the evidence submitted and, accordingly, the preliminary recommendations do not constitute a reasonable or scientifically sound or suitable basis on which to base guidance to the NHS. For the reasons stated above the cost-effectiveness of ranibizumab has been systematically underestimated. Based on the available evidence ranibizumab represents a clinically and cost-effective treatment for patients with all lesion types of wet AMD. Furthermore, the restriction to predominantly classic lesions in the better seeing eye only cannot be justified on scientific, ethical or moral grounds.

## References

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<sup>i</sup> [http://www.rcophth.ac.uk/docs/scientific/publications/IVT\\_Inject\\_Guidelines\\_FINAL\\_for\\_website.pdf](http://www.rcophth.ac.uk/docs/scientific/publications/IVT_Inject_Guidelines_FINAL_for_website.pdf)

<sup>ii</sup> Chang.T *Ranibizumab (Lucentis) Self-reported vision-specific Quality of Life*, ARVO 2006 Subspecialty Day - Retina; Section II: AMD and Pharmacologic Monotherapy P18-20

<sup>iii</sup> Williams et al. The psychosocial impact of macular degeneration. *Arch Ophthalmol* 1998; 116: 514-520

<sup>iv</sup> Brown et al. Quality of life associated with unilateral and bilateral good vision. *Ophthalmology* 2001; 108: 643-648.