

Comments from Novartis Pharmaceuticals UK Limited on the Additional Analyses Pertaining to the Health Technology Appraisal of Ranibizumab for the Treatment of Wet AMD

Thank you for your invitation to comment on the above referenced Additional Analyses, which were released on the 28th September 2007. Novartis are pleased that NICE has seen fit to commission the additional analyses to address concerns raised by Consultees regarding the preliminary recommendations as set out in the ACD, issued on the 7th June 2007.

It is important that when evaluating the Additional Analyses, the Appraisal Committee should take the following factors into account.

1. The Additional Analyses conducted by SHTAC demonstrate that ranibizumab is cost-effective, irrespective of the other assumptions, based on conventionally accepted thresholds, for all lesion types when used in accordance with the licensed dosing regimen. All of the available evidence from clinical trials and routine clinical practice indicate that ranibizumab will require considerably less than twelve injections per year. Therefore the SHTAC base case estimates of cost-effectiveness, which are all based on 12 injections per year, grossly underestimate the cost-effectiveness of ranibizumab. Importantly, ranibizumab was found to be cost-effective in all scenarios which were based on 9 injections in year 1 and 6 injections in year 2 where the resulting incremental cost-effectiveness ratios (ICERs) ranged from around £15-£26k per QALY. In addition, a dosing frequency of 9 injections in year 1 and 6 injections in year 2 is likely to represent a conservative estimate as emerging data from the PrONTO and SUSTAIN studies as well as evidence from practising UK clinicians indicate that the dosing frequency will be around 5 to 6 injections per year, thus improving the cost-effectiveness of ranibizumab even further.

2. The assumption 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. In addition, we do not believe that the costs of blindness have been adequately accounted for within the analyses. The combined impact of the above assumptions will be to underestimate the cost-effectiveness of ranibizumab.

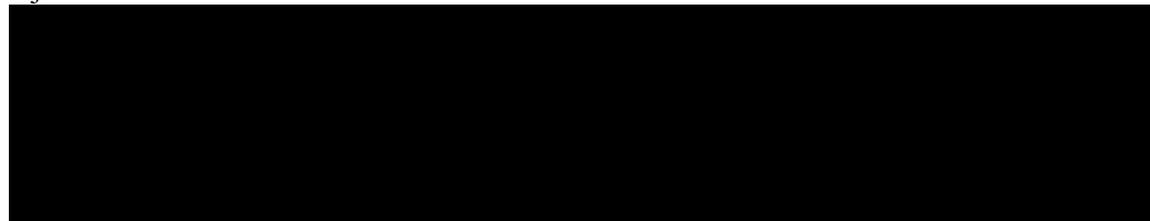
3. There is insufficient evidence to justify limiting ranibizumab treatment to the better seeing eye. In practice, such a restriction will mean that patients will be allowed to go blind in one eye before being eligible for treatment, which is morally and ethically unacceptable. In addition, the anxiety and distress of knowing that that you will be left to go blind in one eye coupled with the possibility that a second affected eye may not be treatable, or may not be treated successfully, will have a considerable detrimental impact on quality of life. This has not been taken into account in any of the estimates considered thus far. No conclusions can be drawn from the SHTAC estimates comparing the cost of treating the first eye versus the

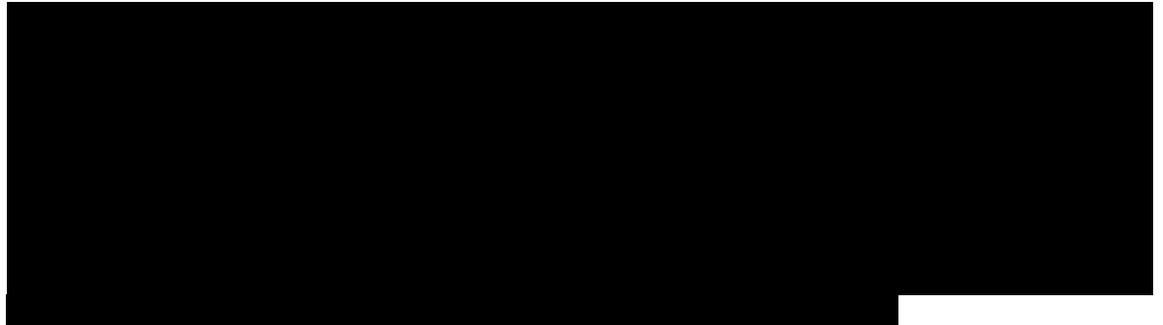
cost of treating both eyes for the following reasons; there is a high degree of uncertainty surrounding the assumptions, insufficient information was provided to validate the estimates and no consideration has been given to the benefits/disbenefits associated with treating the better seeing eye versus treating both eyes.

These points, as well as our other comments, are addressed in more detail below.

1. The Additional Analyses conducted by SHTAC demonstrate that ranibizumab is cost-effective, irrespective of the other assumptions, based on conventionally accepted thresholds, for all lesion types when used in accordance with the licensed dosing regimen. All of the available evidence from clinical trials and routine clinical practice indicate that ranibizumab will require considerably less than twelve injections per year. Therefore the SHTAC base case estimates of cost-effectiveness, which are all based on 12 injections per year, grossly underestimate the cost-effectiveness of ranibizumab. Importantly, ranibizumab was found to be cost-effective in all scenarios which were based on 9 injections in year 1 and 6 injections in year 2 where the resulting incremental cost-effectiveness ratios (ICERs) ranged from around £15-£26k per QALY. In addition, a dosing frequency of 9 injections in year 1 and 6 injections in year 2 is likely to represent a conservative estimate as emerging data from the PrONTO and SUSTAIN studies as well as evidence from practising UK clinicians indicate that the dosing frequency will be around 5 to 6 injections per year, thus improving the cost-effectiveness of ranibizumab even further.

The base case estimates for ranibizumab presented in the Assessment Report, Additional Analysis and Addendum all assume 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 base case 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. As detailed in our response to the ACD, dated 11th July, 2007, 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 ≥ 15 letters in 43% of patients. These results have now been published and 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.ⁱ





The Additional Analysis presents a number of scenarios assessing the impact of a reduced dosing frequency. All scenarios which are based on 9 injections in year 1 and 6 injections in year 2 result in ICERs ranging from £14.7k to £25.2k per QALY. It should be noted that the highest ICER of £25.2k/QALY is based on conservative assumptions using unvalidated costs provided by the Royal College. Moreover emerging data indicates that in practice patients will require 5 to 6 injections per year. Scenarios which are based on 6.5 injections in year 1 and 3.5 injections in year 2 result in ICERs which are below £20k/QALY under all assumptions tested. This demonstrates that ranibizumab is cost-effective based on conventionally accepted thresholds for minimally classic, occult and predominantly classic lesions with an ICER less than £25.2k/QALY assuming 9 injections in year 1 and 6 injections in year 2 and an ICER less than £20k/QALY assuming 6.5 injections in year 1 and 3.5 injections in year 2.

In summary, the Additional Analyses demonstrate that ranibizumab is cost-effective, based on conventionally accepted thresholds, for all lesion types when used in accordance with the licensed dosing regimen.

2. The assumption 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. In addition, we do not believe that the costs of blindness have been adequately accounted for within the analyses. The combined impact of the above assumptions will be to underestimate the cost-effectiveness of ranibizumab.

Day case procedure costs vs. outpatient visits.

As set out in “The Royal College of Ophthalmologists Intravitreal Injections Procedure Guideline”ⁱⁱ, 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. In practice it is unlikely that all injections will be administered as a day case procedure and unrealistic to assume that there are adequate resources available to do so.

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 view is also held by the RNIB. Comments from the RNIB and Andrew Lotery are referred to on page 19 of the Additional Analysis Report which lists a number of cost of blindness factors which Consultees felt should have been accounted for in the original estimates. It is noted that these factors have largely been assessed on an individual basis, within the sensitivity analysis, where varying each factor on its own results in a relatively small reduction on the overall ICER. However, the most plausible assumptions should be considered together to assess their combined impact, as, whilst consideration of each factor individually may only result in a small reduction in the ICER, the combined impact of the most plausible assumptions is likely to have a larger and more significant impact.

In summary, if the estimates of cost-effectiveness are revised to take into account all of the appropriate costs of blindness and a more realistic cost for ranibizumab administration ie less than 100% day case costs, the ICERs presented in the Addendum for ranibizumab will be less than £21,043 per QALY based on 9 injections in year 1 and 6 injections in year 2. This provides additional support for the view that ranibizumab is likely to be cost-effective for all lesion types based on the licensed dosing schedule.

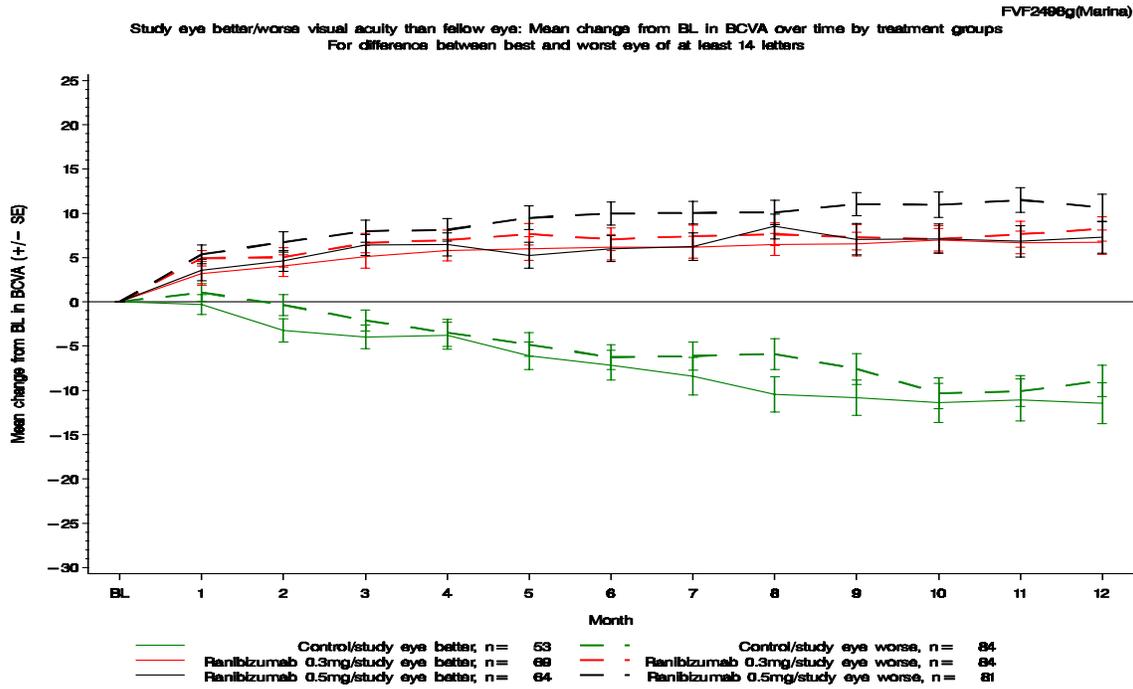
3. There is insufficient evidence to justify limiting ranibizumab treatment to the better seeing eye. In practice, such a restriction will mean that patients will be allowed to go blind in one eye before being eligible for treatment, which is morally and ethically unacceptable. In addition, the anxiety and distress of knowing that that you will be left to go blind in one eye coupled with the possibility that a second affected eye may not be treatable, or may not be treated successfully, will have a considerable detrimental impact on quality of life. This has not been taken into account in any of the estimates considered thus far. No conclusions can be drawn from the SHTAC estimates comparing the cost of treating the first eye versus the cost of treating both eyes for the following reasons; there is a high degree of uncertainty surrounding the assumptions, insufficient information was provided to validate the estimates and no consideration has been given to the benefits/disbenefits associated with treating the better seeing eye versus treating both eyes.

Tables 1 to 8 of the Additional Analysis Report present the estimated costs for treating one or both eyes. However, it is difficult to validate and comment on these estimates as insufficient information is provided in the report on the time horizon and breakdown of costs. In addition, no detail is given as to how the costs for all lesion types have been combined to give one estimate of costs for ranibizumab.

Moreover, no estimates of the expected outcomes have been presented due to the high level of uncertainty and complex nature of the underlying disease. There is therefore insufficient evidence to justify a restriction of treatment to the better seeing eye.

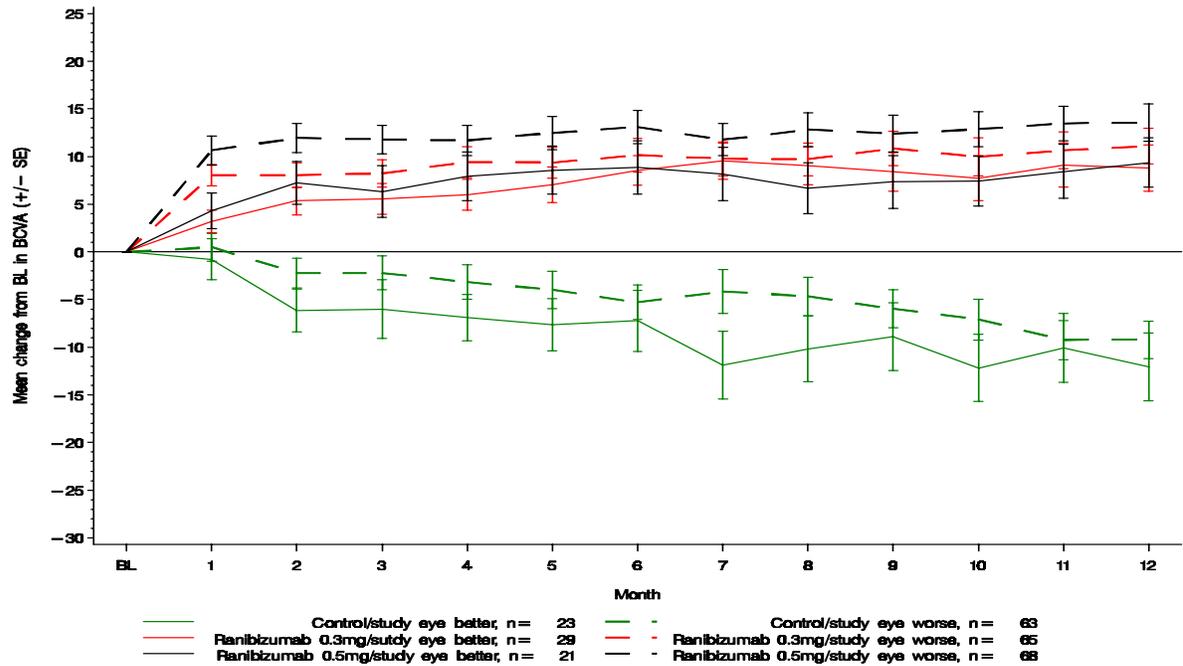
Patient reported outcomes from MARINA and ANCHOR demonstrate statistically significant and clinically meaningful improvements in near activities, distance activities, and vision-specific subscales of the VFQ-25 instrument. These benefits were

demonstrated regardless of whether patients received ranibizumab in the better- or worse seeing eye.ⁱⁱⁱ 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.



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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.^{iv} 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.^v 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 relative benefits of binocular and monocular vision, and the distress caused by an untreated affected eye should be taken into account when formulating the final recommendations. There, 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. As detailed in our comments on the ACD, dated 12.7.07, Novartis conducted a survey involving 47 ophthalmologists who have considerable experience with ranibizumab. The majority (88%) of the ophthalmologists responding to our survey were of the view that it would be unethical to restrict treatment to the better seeing eye.

Other comments

Page 27, Costs from Royal College of Ophthalmologists

It is not clear from the College Guidelines how all of the costs specified relate to NHS reference costs. In addition, the categories provided by the College are not specific enough to validate whether they justify inclusion within the economic analysis, for example it is not clear what “non-pay” costs and “PTS” costs are and whether they warrant inclusion in the economic analysis. We agree with the adjustments made by SHTAC to remove VAT from the drug costs and to adjust the overheads to non-drug costs only. However, it should be noted that there may be an element of double counting if overheads were already included in some of the unit costs.

In summary, there is insufficient information to validate the costs provided by the College to ensure that only appropriate costs are taken into account in the cost-effectiveness analysis. Therefore these costs should not be used to form the basis of recommendations to the NHS.

Page 33, Tables 43-45

Additional sensitivity analyses were conducted to assess the impact of using alternative sources for the health utility states. This included using utility values from a study by Espellargues *et al.* This study was conducted in patients using the HUI-3 preference based utility instrument. However, the HUI-3 only uses a crude generic description of visual function that is not sensitive enough to reflect the specific impact of wet AMD on health related quality of life. Therefore this study does not provide an appropriate source of utility values for this appraisal. This is further supported by the fact that none of the economic modellers either academic or commercial have deemed this an appropriate source of utilities for any of the wet AMD NICE technology appraisals.

In summary, the Additional Analysis conducted by SHTAC demonstrates that ranibizumab is cost-effective, based on conventionally accepted thresholds, for all lesion types associated with wet AMD when administered in accordance with its licensed dosing schedule. Furthermore, the restriction to treatment in the better seeing eye only cannot be justified on scientific, ethical or moral grounds.

References

ⁱ Lalwani, G. All about PrONTO: Study Yielded Good Results in AMD with Treatment Guided by OCT. *Retina Today* 2007; May/June p41-48

ⁱⁱ http://www.rcophth.ac.uk/docs/scientific/publications/IVT_Inject_Guidelines_FINAL_for_website.pdf

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

^{iv} Williams et al. The psychosocial impact of macular degeneration. *Arch Ophthalmol* 1998; 116: 514-520

^v Brown et al. Quality of life associated with unilateral and bilateral good vision. *Ophthalmology* 2001; 108: 643-648.