

**Comments from Novartis Pharmaceuticals UK Limited on the Appraisal
Consultation Document (ACD) 2, dated December 2007, 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) 2, received on 7th December 2007. Novartis welcomes the development of a new ACD and the opportunity to comment on the preliminary recommendations.

We are pleased that the preliminary recommendations will allow patients with all wet AMD lesion types, affecting either eye, to benefit from treatment with ranibizumab in accordance with its licensed recommendations. In addition, we welcome the opportunity to collaborate with the Institute and the Department of Health to facilitate patient access by capping the dose of ranibizumab. A summary of the proposed dose capping scheme is provided in Appendix 1.

Some further comments are detailed below regarding the recommendation limiting treatment to best-corrected visual acuity better than 6/60 and interpretation of the evidence.

Recommendations, Section 1.1, 1st bullet point, page 3

This recommendation states that the eye to be treated should have a best-corrected visual acuity better than 6/60. Section 4.3.23 states that this is appropriate because the majority of the trial participants had a visual acuity above 6/60 and 6/60 is the level where a person is considered to be legally blind in the UK. However, it should be noted that 6/60 is the threshold for being considered partially blind.

In addition, a total of 74 patients with a baseline visual acuity of <6/60 were entered into the ranibizumab trials (cross the three Lucentis studies (MARINA n=27, ANCHOR n=34 and PIER n=13). Results from these studies demonstrate that some patients with visual acuity below 6/60 at baseline had improved to visual acuity >6/60 ie some useful vision, by month 3 and month 12. These results are presented in the table below.

Table 1 – Visual Acuity Outcomes in Patients with a Visual Acuity of <6/60 at Baseline Following 3 and 12 Months of Treatment

	Baseline v.a <6/60 (n)	Month 3 with v.a >6/60 % (n)	Month 12 v.a with v.a >6/60 % (n)
MARINA ranibizumab	(12)	36% (4)	42% (5)
MARINA sham	(15)	20% (3)	27% (4)
ANCHOR ranibizumab	(15)	47 % (7)	33% (5)
ANCHOR control	(19)	32% (6)	20% (4)
PIER ranibizumab	(8)	50% (4)	50% (4)
PIER sham	(5)	40% (2)	40% (2)

Although the numbers of patients are too small to draw any firm conclusions, the data suggest that patients with a visual acuity of 6/60 or below may have the potential to obtain benefit from ranibizumab treatment. We therefore propose that the recommendation is amended to allow patients with a visual acuity of 6/60 or better in the affected eye are able to receive treatment.

Section 4.3.8, page 23

This section states,

“It heard from clinical specialists that it is unclear how long treatment would be continued in practice, that there is an evolving evidence base, and that for some patients it would be appropriate to continue treatment beyond 2 years into the third or even fourth year. This would result in additional drug, administration and monitoring costs, which were not included in any of the economic models.”

However, it should be noted that treatment would only be considered beyond two years if it were deemed by the clinician that the patient had a capacity to benefit. Therefore any analysis of cost-effectiveness beyond two years would need to take into account both the additional benefits as well as costs.

Sections 4.3. 10 and 4.3.21, on pages 24 and 29

These sections of the ACD state,

“However, the Committee remained concerned about the assumption that the benefit achieved in the pivotal trials could be matched with lower doses.”

“The Committee discussed the number of injections of ranibizumab assumed in the model. It noted that if 8 injections would be required in the first year and 6 in the second, as suggested by consultees (see section 4.3.10), ICERs would be substantially lowered. However, it considered that many patients would be likely to require more injections than this to maintain benefit.”

The statement that many patients would be likely to require more than 14 injections to maintain the level of benefit observed in clinical trials is purely speculative. Furthermore, all of the available evidence does not support this view. As detailed in our previous submissions, 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 are published and are similar to those observed in the MARINA and ANCHOR studies and were achieved with an average of 9.9 injections over 24 months.ⁱ In addition, emerging data from an interim analysis of 75 patients participating in SUSTAIN, an open label, prospective trial, using the licensed PRN dosing frequency, demonstrate a mean improvement in visual acuity of 6.5 letters at 12 months. These improvements in vision were achieved with 0.3mg ranibizumab and are comparable to the 12 month results from the 0.3mg arm of the MARINA study (6.5 letter gain). The SUSTAIN results were achieved with an average of 5.3 injections over the course of 12 months. It should be noted that this dose is lower than the UK licensed dose of 0.5mg. Based on results from other ranibizumab trials, including MARINA and ANCHOR, which evaluated both 0.3mg and 0.5mg, we would expect greater improvements in vision with 0.5mg than 0.3mg. Therefore initial results from the SUSTAIN trial indicate that the levels of vision improvement observed in the ANCHOR and MARINA trials can be achieved with 5 to 6 ranibizumab injections per year using the pragmatic, dosing regimen recommended in the SmPC at the recommended dose of 0.5mg.

Section 4.3.11, page 25

The ACD states,

“...the assumption that no-one would receive further injections after 2 years was not probable.”

The current evidence base clearly demonstrates that 15 doses of ranibizumab given over a two-year treatment period are cost-effective for the treatment of patients with wet AMD. There are insufficient data at present to determine how many injections may be required beyond two years, although we do know that this will vary from patient to patient based on individual responses. However, where injections are given beyond two years the decision to treat will be based on potential benefit. Therefore benefits and costs beyond two years should be evaluated as and when appropriate data are available. Guidance should be based on the available evidence and not on speculation as to what may or may not happen beyond the current timeframes.

Section 4.3.21, page 29

The ACD states,

“Additionally, continued administration and monitoring costs would also need to be considered as patients would require regular re-assessment on a monthly basis to monitor the progress of their disease.”

It should be noted that the additional analysis conducted by SHTAC, dated 21st September 2007, includes an analysis which takes into account the monthly monitoring costs. The results of this analysis demonstrate that ranibizumab is cost-effective based on 15 injections administered over a two year period with a cost per QALY gained of £14,704 (See Table 41, page 33).

Implications for the NHS

As acknowledged in Guidance TA No.68 relating to photodynamic therapy, wet AMD can progress rapidly. Therefore, it is important that patients receive treatment early in order to retain as much vision as possible. In order to facilitate this, we propose that wording similar to that presented in Section 6.2 of Guidance TA No.68 is also included in the guidance for this appraisal,

“For treatment to be as effective as possible, individuals with wet AMD should be fast tracked through the referral and waiting list processes in order to receive treatment before further loss of vision occurs.”

In summary, although we do not entirely agree with all of the interpretations of the evidence, we believe that in general the recommendations represent a sound basis on which to provide guidance to the NHS. We welcome the opportunity to collaborate with the Institute and the Department of Health to define a scheme which will facilitate patient access to ranibizumab.

Details of the proposed scheme are attached as Appendix 1.

References

¹ Lalwani, G. All about PrONTO: Study Yielded Good Results in AMD with Treatment Guided by OCT. Retina Today 2007; May/June p41-48