

## Response to NICE consultation on pegaptanin and ranibizimab for ARMD on behalf of **Derbyshire County PCT**

As I explained in my email, due to the restructuring of PCTs the opportunity for this PCT to comment in the first round of consultations was lost. The following comments are therefore broad.

Ranibizumab is undoubtedly an extremely effective drug, dramatically so, and as such very different from the many marginally effective cancer drugs.

It is VERY expensive. Any analysis will therefore depend very much on the quality of the economic appraisal. This is problematic as the underlying data is poor and subject to enormous uncertainties. The loss of quality of life being quoted is based on research on (unrepresentative) clinic attendees whereas other sources point to a lesser impact (<http://www.mdsupport.org/library/summary2007.html> (August 2006))\*.

ARMD causes central blindness and whilst that is crucial for many important functions, peripheral vision is not lost so objects are not collided with and stairs can be managed: extensive cataracts or severe diabetic retinopathy are worse. However the assessments of gains in QoL over the 10 year horizon are relatively large for both ranibizumab and best care with any small error for an individual year multiplied up. There is therefore considerable scope for a systematic error in the estimate of the marginal benefit of ranibizumab that neither the deterministic nor probabilistic sensitivity analyses address. If the loss of QoL were to be ascertained from the majority of the 260,000 cases of wet ARMD in the UK, especially those who have adjusted to severe loss of vision, then the loss might be rather less than that derived from the clinic samples. This would have a significant impact on ICER calculations if as is likely the bulk of ARMD cases will eventually end up on treatment.

The assumptions being made are that treatment will cease at 2 years. This will not happen nor should it. It would be unethical to cease treatment when at 2 years patients on treatment would be clinically indistinguishable from new cases. Furthermore by 2 years the cost effectiveness of each additional injection will be at its height and, unless the effects of the drug decline, will continue to rise (until the eyesight of the equivalent control cohort would have declined beyond effective use). Please see the attached graphical representation at the end. The area in the red box represents the QALY gain from ranibizumab in the second year (with each 5 letter loss below the baseline representing twice as much QALY loss as above baseline) and is much larger than the blue box for the first year. Unless sight deteriorates significantly on ranibizumab after year 2 (there looks to be a small decline after around month 18) subsequent annual blocks would be even larger than the red box with the control arm continuing to decline at least until 6/60 (when treatment should stop). I estimate that in year 3 there would be a gain of 0.24 QALYs over control (minus that from best supportive care) compared to 0.1 QALY in year 1. Costs in year 1 are higher: under PRONTO/licence regimen it would be for 3+ 2.5 injections compared to 3.5 in years 2 and 3).

The most likely clinical behaviour is to continue after 2 years. NICE should have modelled this scenario to calculate the ICER in real life use.

The 10 year horizon economic analysis is based on an assumption that once ceased decline continues as per control arm after about 6 months. The rate of decline in sight for the control arm would suggest that it would take about 3 to 4 years at most to reach loss of useful sight, though in MARINA the curve looks to be reaching a

plateau at 2 to 3 years at between 6/48 and 6/60, perhaps reflecting a stable end point to progression in a population. However, either way there will be little health gain beyond 7 years and if the model does suggest significant gain beyond then it is suspect. The favourable ICER using the model is the result of the benefits of delayed progression over a few years at no additional treatment cost. The effect would be demonstrated by copying the control curve in the attached by some 2.5 years to the right and up 6 letters with the gap representing the benefit. In fact this favourable ICER would probably be maximised if treatment ceased at 3 months at which point the maximum improvement in sight and separation of the curves is reached at least cost (the copied control curve starting at 9 months and +5 letters to represent continuation of the ranibizumab curve).

The PIER study using 3 monthly injections followed by an injection every 3 months showed a marked decline in visual acuity compared to MARINA/ANCHOR. It would seem unlikely that, given the short half life of ranibizumab, that its effects would last much beyond 4-6 months after cessation of treatment.

Loss of QoL as the disease progresses is variable, dependent on the level of visual acuity according to the assessment report. Between 6/60 and 3/60 only an additional 0.05QALY is lost. The MARINA trial showed in fig 2c that there is no **improvement** in acuity for those with a starting acuity 6/60 or worse, though there was a small improvement in ANCHOR (fig 1d). The major improvements in acuity are obtained in those patients early in the disease with acuity 6/12 or better (MARINA fig2b; ANCHOR fig 1c). These findings are biologically plausible. These two issues combined should result in a policy that excludes patients with visual acuity worse than 6/60, both in terms of starting treatment and cessation criteria. This is identified in the new economic assessment but NICE is urged to restrict treatment to better than 6/60 both in start AND cessation criteria. NICE should recommend that efforts are made to ensure early diagnosis thus ensuring maximum benefit from this drug.

The PRONTO study reported an interesting individual case:

**Patient 037**

*A 76 year old woman with an occult neovascular lesion consistent gained 15 letters by Month 3 compared with baseline. She gained a total of 34 letters through Month 24, achieving a visual acuity of 20/16. She required only the first 3 scheduled injections, receiving no reinjections through Month 24.*

The implication of this is that, as such patients have contributed to the average, other patients will have had lesser benefits. A cessation criteria based on rate of decline of vision despite further injections (say at the same rate as the average for the control arm, eg 5 letters in 8 months) would therefore seem appropriate as such patients will require the costliest treatment for the least gain.

Patients will require treatment for an average of 10 years. Even if the annual costs were just £2000 on average, a treatment cohort would rise over 10 years to 230,000 costing nearly £0.5bn or 0.65% of current NHS PCT allocations for this one non-fatal disease. Indeed, there is already a cohort with ARMD with visual acuity better than 6/96 which is substantially larger than 23,000. Using ranibizumab in accordance with its licensed regimen in **one** eye of all ARMD patients could cost £1-2bn. The treatment, effective and desirable as it may be, is unaffordable. NICE 'does not do affordability' ... but it **must** consider it in this case.

Second eye:

Many people function adequately with monocular vision especially those with lifelong amblyopia: driving is possible. The loss of QoL from the absence of binocular vision is small. Treating first eye with ranibizumab therefore represents an 'insurance policy'

and any cost effectiveness calculation should be based on the number needed to treat to avoid blindness in both eyes and the loss of QoL associated. Nevertheless whilst there is a first eye policy for PDT under TAG 68, though only for classic disease, given that ranibizumab is so much better, this does not sit well as a policy. How does the consequences of a *first eye only* policy (ie do not treat second eye, or switch to second eye, should it become affected but has better acuity) compare?

Pegaptanib looks to be very much second best, as does PDT against ranibizumab.

Finally, once again NICE is looking at thresholds beyond its lower limit of £20k/QALY. Setting aside the general debate over the threshold (indeed any threshold) as discussed in the BMJ of 25<sup>th</sup> August, why has NICE chosen to consider higher thresholds for a non-life threatening condition? Can NICE give EXPLICIT reasons?

Research:

NICE should be recommending urgent research into the frequency of follow up under the 'test and treat' regimen. Are there any predictors of the rate of decline (and thus frequency of injections; does a pattern of frequency of injections for an individual patient become clear? The answers to these questions could reduce frequency of follow up and thus a substantial element of costs. IVAN, to start in January has two comparative arms: monthly treatment or 3 monthly injections followed by further cycles of 3 monthly injections. The PRONTO regimen and that described in the Product licence is for 3 monthly injections followed by review with deterioration triggering another injection: this, if effective, would be cheaper than the second arm of IVAN and should form a third arm within IVAN. Were IVAN to be larger (than 300) it could answer some important questions very quickly and most PCTs would be willing to participate.

The outcomes in PRONTO case 037 suggest that wet ARMD is not fully understood as these outcomes are not consistent with a progressive chronic disease or the mode of action of anti-VEGFs. This response would be that expected in a self-limiting/acute disease. Careful consideration of the course of individual cases needs to be undertaken to improve our understanding of this disease, which may more than just one in reality.

Bevacizumab:

***NICE has refused to consider bevacizumab as it is not licensed for ARMD. However NICE has recommended PDT using verteporfin for classic with no occult wet ARMD in TAG 68, whilst not recommending it for predominantly classic wet ARMD. The licence for verteporfin is for the treatment of predominantly classic wet ARMD not classic wet ARMD (and Novartis recently asked for its licence for occult ARMD to be rescinded). This is not consistent.***

***\*Age-related Macular Degeneration Does Not Cause Blindness***

*A poll sponsored by MD Support shows that a strong majority of people affected by AMD do not think of themselves as blind, and they do not want the term to be used to describe their visual impairment.*

*The results of a recent MD Support opinion survey show that 93% of people with AMD are averse to the use of the word "blind" in connection with their condition. 91% of them do not consider themselves to be blind, 93% know they will not go blind from AMD and 93% think the word by itself should not be used in connection with AMD. These are convincing statistics that are now available for the first time to eye care professionals, patient advocacy organizations and public service agencies. Hopefully, the message is clear and will be heeded.*

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Derbyshire County PCT

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**24 October 2007**

Attachment

