

Comments from Novartis on the Assessment Report for the Health Technology Appraisal of Pegaptinib and Ranibizumab for the treatment of age-related macular degeneration

In general we feel that the Assessment Report is a fair and accurate representation of the evidence base. However, there are a few important issues which need to be highlighted. These issues can be summarised as follows;

- 1. Ranibizumab received marketing authorisation on the 22nd January 2007 and was launched in the UK on the 12th of February with a price for a single use vial of £761.20 ex. VAT.**

The recommended posology is now clearly defined and represents a pragmatic and clinically directed approach to dosing. This means that the estimates from the Assessment Group's model underestimate the cost-effectiveness of ranibizumab as they are based on the maximum dose ie 12 injections per year. In routine clinical practice the dose of ranibizumab will be individualised to achieve maximum benefit with minimum dosing.

The CHMP approved Summary of Product Characteristics (SmPC) stipulates that the interval between doses should be no shorter than 1 month and therefore the maximum number of injections that patients can receive in any one year is 12. Evidence from the drug and disease model (detailed in our submission) suggests that patients will receive on average 8 injections in the first year and 6 injections in the second. The decrease in costs associated with the reduced dosing schedule means that ranibizumab will be more cost-effective than current estimates from the Assessment Group's model suggest.

- 2. Results from the MARINA and ANCHOR studies demonstrate that ranibizumab improves vision by a clinically significant amount (>15 letters gained) in 34-40% patients versus 5-6% in the control groups. Whilst there are no direct head to head comparisons between ranibizumab and pegaptinib, it is important to note that pegaptinib improved vision in only 6% of patients versus 2% in the control group in the VISION trial. The last sentence of the "Background" section on page 10, of the Assessment Report is misleading as it implies that the scale of vision improvement is the same for both products. This is not supported by the current evidence base and therefore the statement should be amended accordingly.**
- 3. The section on suggested research priorities highlights the fact that bevacizumab is "biologically similar" to ranibizumab. This could mistakenly be taken to imply therapeutic equivalence. This is extremely misleading as there is currently no robust clinical evidence to establish the clinical effectiveness of bevacizumab for wet AMD.**

These issues are covered in more detail below.

1. Ranibizumab received marketing authorisation on the 22nd January 2007, subsequent to our submission. The recommended posology is now clearly defined and represents a pragmatic and clinically directed approach to dosing. This means that the estimates from the Assessment Group's model underestimate the cost-effectiveness of ranibizumab as they are based on the maximum dose ie 12 injections per year. In routine clinical practice the dose of ranibizumab will be individualised to achieve maximum benefit with minimum dosing.

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The approved SmPC recommends the following dosing schedule, “Ranibizumab treatment is initiated with a loading phase of one injection per month for three consecutive months, followed by a maintenance phase in which patients should be monitored for visual acuity on a monthly basis. If the patient experiences a loss of greater than 5 letters in visual acuity (ETDRS or one Snellen line equivalent), ranibizumab should be administered. The interval between two doses should not be shorter than 1 month.” This reduced dosing schedule is in line with actual routine usage in the U.S. as well as data from the PrONTO study which showed that a clinically directed re-treatment criteria may reduce dosing to a mean of 5.5 treatments a year, but still maintain a mean change of +9.3 letters over 12 months (also detailed in our submission). The results from this study are comparable to those observed in the MARINA and ANCHOR studies.

The MARINA and ANCHOR studies (based on monthly dosing), showed statistically significant benefits in favour of ranibizumab for all the vision outcomes evaluated including an unprecedented improvement in vision. The PIER study (with monthly dosing for the first 3 months followed by one injection every 3 months) met its primary endpoint, maintenance of vision thus confirming the efficacy of ranibizumab in all subtypes of wet AMD. However, the improvements in visual acuity seen at 3 months in the PIER study were not sustained out to 12 months in the population taken as a whole, although visual acuity had stabilised (<5 letters lost from baseline).

Results from the PIER study demonstrate that vision improvement attained at 3 months was maintained out to the point prior to the next injection 3 months later in 49% of patients (i.e. although an injection was subsequently administered, the patient had no change in vision since the last injection and thus did not require this therapy). This suggests that a fixed dosage regimen may not be appropriate for all patients as a proportion of patients in PIER were over-treated whilst some required the dose frequency to be more intensive than the quarterly period. The differences in efficacy seen at the end of the three studies have suggested that an individualised dosing frequency between monthly to quarterly during the maintenance phase, could maximise visual acuity benefits (cf. MARINA and ANCHOR) but with as few as possible treatments (cf. PIER).



In summary, the estimates of cost-effectiveness for ranibizumab generated by the Assessment Group's model are conservative as in practice patients are likely to receive less than 12 ranibizumab injections per year. The base case estimates of £15,638 per QALY for predominantly classic lesions vs PDT, £11,412 per QALY for predominantly classic lesions vs best supportive care (BSC) and £25,098 per QALY for minimally classic and occult lesions all demonstrate that ranibizumab is cost-effective based on a willingness to pay threshold of £30,000. This conclusion is confirmed by results from the probabilistic sensitivity analyses for all lesion types. However, these results underestimate the cost-effectiveness of ranibizumab based on the decreased dosing frequency to be used in routine practice.

- 2. Results from the MARINA and ANCHOR studies demonstrate that ranibizumab improves vision by a clinically significant amount (>15 letters gained) in 34-40% patients versus 5-6% in the control groups. Whilst there are no direct head to head comparisons between ranibizumab and pegaptanib, it is important to note that pegaptanib improved vision in only 6% of patients versus 2% in the control group in the VISION trial. The last sentence of the "Background" section on page 10, of the Assessment Report is misleading as it implies that the scale of vision improvement is the same for both products. This is not supported by the current evidence base and therefore the statement should be amended accordingly.**

The scale of vision improvement with ranibizumab is an order of magnitude greater than that seen with pegaptanib.

Ranibizumab in the MARINA & ANCHOR studies, has been shown to improve visual acuity by a clinically significant amount (>15 letters gained) in 33-40% of patients, which was highly statistically significantly different ($p < 0.0001$) versus comparators (sham 4.6% or PDT 5.6%). Pegaptanib 0.3mg in the VISION study has been shown to improve visual acuity by a clinically significant amount (>15 letters gained) in 6% of patients that only just reached statistical difference ($P = 0.04$) versus sham (2%).

The NNT for 1 patient to gain 15 letters of vision with pegaptanib is thus 25, whereas the NNT for 1 patient to gain 15 letters of vision with ranibizumab is 3.4 versus sham (minimally classic and occult lesions) and 2.88 versus PDT (predominantly classic).

- 3. The section on suggested research priorities highlights the fact that bevacizumab is "biologically similar" to ranibizumab. This could mistakenly be taken to imply therapeutic equivalence. This is extremely misleading as there is currently no robust clinical evidence to establish the clinical effectiveness of bevacizumab for wet AMD.**

Under suggested research priorities, the report suggests that bevacizumab is biologically similar to ranibizumab and infers "therapeutic equivalence". This is used to justify the proposed HTA Clinical Trials Programme of a head-to-head study of ranibizumab and bevacizumab.

It was Novartis' understanding that the scope of this appraisal is to discuss the clinical and cost-effectiveness of ranibizumab and pegaptanib for the treatment of wet AMD, against appropriate comparators. Bevacizumab is not an appropriate comparator as the current level of evidence for bevacizumab in patients with wet AMD, is derived from case series that are

in general, based on small-scale, uncontrolled, retrospective analyses, with short-term and non-systematic follow-up.

Importantly, the bevacizumab evidence base lacks the following:-

1. Formal ocular toxicology and pharmacology studies in pre-clinical models of eye disease;
2. Formal phase I dose-ranging studies, to establish minimum effective or maximum tolerated doses in humans, that evaluate the proposed intravitreal dose for use in subsequent human clinical studies,
3. Formal clinical pharmacology studies to establish pharmacokinetic and pharmacodynamic parameters for single and multiple doses in the eye; and
4. Formal randomised, controlled phase II studies to validate evidence of therapeutic benefit and risks, over a control group, in the disease to be tested.

In the absence of such critical data, the use of bevacizumab in a large phase III head-to-head study versus ranibizumab, would expose large numbers of patients over a long period of time to a drug for use in a disease state where the benefit:risk ratio has not been explored in a systematic and scientific manner.

Thus such a head-to-head study should not be part of any future research priority that forms part of this NICE appraisal. Further, there are a number of differences between the two molecules that may result in differences in potential therapeutic benefit:-

- Ranibizumab is an antibody fragment (Fab) of approximately 50 kDa in size, where as bevacizumab is a full length antibody that includes the Fc portion and is approximately 150kDa in size
- Ranibizumab binding affinity for VEGF-A isoforms is significantly greater than bevacizumab
- Ranibizumab has a very short half-life systemically (2 hours) when administered by intravitreal injection, whereas the only data that is available for bevacizumab suggests a half-life of 21 days when administered systemically.

Page 19, Discussion, last paragraph

This section states,

“The validity of assumptions underlying our extension from trial results to ten years may be open to question.”

The “Guide to the Methods for Technology Appraisal” states,

“The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect important cost and benefit differences between the technologies being compared.....”

Treatments for wet AMD have impacts on costs and outcomes over a person’s lifetime therefore a ten year time horizon is valid and reasonable, representing the approximate life expectancy for a patient in their mid-seventies. This is acknowledged in the Assessment Report. Ranibizumab delays progression to blindness which incurs one of the major costs associated with wet AMD. It

is therefore important that the time horizon is adequate to capture the impact of delaying this important and costly outcome.

Page 20, Suggested Research Priorities, bullet point 2.

This section states,

“Pegaptanib is clinically effective for delaying vision loss associated with AMD. Although the proportion of patients experiencing improvements in vision appears less with pegaptanib than ranibizumab, no head to head RCTs have been conducted. A trial comparing pegaptanib with ranibizumab and bevacizumab is recommended. The role of verteporfin PDT in combination with these drugs should also be investigated.”

For the reasons stated above for ranibizumab, the comparison of bevacizumab versus ranibizumab and/or pegaptanib is inappropriate.

There are ongoing studies examining the role of PDT with ranibizumab, being sponsored by Novartis. 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 is planned to commence in March 2007 with a recruitment target of 250 patients.

The study’s primary objectives are as follows:-

- To demonstrate that verteporfin-PDT combination therapy is not inferior to ranibizumab monotherapy with respect to the mean change from baseline in Best-Corrected Visual Acuity (BCVA) letter score at Month 12.
- To evaluate the proportion of patients with a treatment-free interval of at least 3 months duration at any timepoint following the loading phase.

The secondary objectives are as follows:

- To demonstrate that the combination therapy is superior to monotherapy, based on the number of ranibizumab re-treatments.
- To evaluate the time to first re-treatment of ranibizumab by comparing verteporfin-PDT combination therapy with ranibizumab monotherapy following the loading phase.
- To assess the safety of verteporfin-PDT combination therapy compared to ranibizumab monotherapy as assessed by ophthalmic and vital signs evaluations and AEs over 12 months.
- To evaluate the efficacy of verteporfin-PDT combination therapy compared to ranibizumab monotherapy on BCVA changes from baseline over 12 months.
- To evaluate the efficacy of verteporfin-PDT combination therapy compared to ranibizumab monotherapy on changes in angiographic and optical coherence tomography (OCT) outcomes from baseline over 12 months.
- To assess the mean change from baseline in BCVA at Months 1, 2 and 3 to evaluate the onset of effect.

A randomised clinical study examining the effects of pegaptanib in combination with verteporfin-PDT versus pegaptanib alone (EOP-1012) was stopped in 2006 due to no differences seen in the efficacy between the 2 arms.

Page 20, Suggested Research Priorities, bullet point 3.

This section states,

“A study to assess adverse events outside the proposed RCTs is also required.”

Ranibizumab adverse events will be routinely collected as part of spontaneous adverse event reporting and as part of normal post-marketing surveillance. No additional studies have been requested from the regulatory authorities as part of routine risk management procedures.”

Page 20, Suggested Research Priorities, bullet point 4.

This section states,

“Further research is required on the optimal dosing regimes of these drugs and the benefits of re-treatment after initial treatment.”

There are ongoing studies examining the role of optimising ranibizumab treatment and the required re-treatment criteria, being sponsored by Novartis. The SUMMIT Mont-Blanc study described above will address many of the questions posed.

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.

The study’s primary objectives are as follows:-

- To provide safety and efficacy data of ranibizumab in patients with subfoveal CNV secondary to AMD using a guided individualised PRN dosing schedule.
- The key secondary objectives are:
 - Mean change in best corrected visual acuity (BCVA) from Baseline to Months 3 and 12
 - Mean change in retinal thickness from Baseline to Months 3 and 12
 - Time to the first re-treatment and the total number of treatments

Page 44, Anticipated costs associated with intervention

This section states,

“At a current exchange rate of 1 US dollar to 0.5354 pounds sterling the UK cost of ranibizumab would be £1,044 per injection.”

Please note that since the Assessment Report was written the price of ranibizumab has been finalised at £761.20 per injection. This was the price used both in the Novartis and SHTAC model.

Page 116, 2nd paragraph

This section refers to the fact that the costs of concomitant triamcinolone injections were included for a proportion of patients receiving PDT in the model.

Costs for concomitant medication including triamcinolone injections were based on expert opinion regarding concomitant drug use in routine clinical practice.

Page 116, 3rd paragraphs

This section refers to the fact that the costs of sham injections were included in the model for comparisons vs BSC. This statement is misleading as the costs of administering sham injections were not included in the model. The costs included in the model relate to the costs of adverse events associated with the administration of the sham injection or PDT. We concur that the costs of adverse events associated with the sham injections should not in practice be included. However, the costs of adverse events associated with PDT are valid costs which are relevant for the comparisons of ranibizumab to PDT for predominantly classic lesions. The sensitivity analysis presented on page 121 for predominantly classic lesions in Table 4.11, (b) i) is therefore invalid.

Page 117, Data inputs, 1st paragraph

This section states,

“The derivation of transition probabilities is unclear in the report.....”

The transition probabilities were derived using a multinomial logistic regression model. The state that each patient remained in was calculated for each quarter (worst state each quarter = highest value 1-5 each quarter), starting from the index date (first examination). Starting from quarter 2, for each patient and each quarter the state of the previous month could be calculated. For the first quarter, the index state (=state at index visit) was considered to be previous state.

These data were then entered into a multinomial logistic regression model: the dependent variable was the current state, and the independent variables (predictors of the current state) were: previous state (to obtain the transition probabilities), year after index date (first year vs. second year data), study treatment group (control vs. case), and all first-level interaction effects between the 3 variables (3 interaction effects). The regression model determined the extent to which separate transition probabilities were required in function of ‘time since index date’ to validly predict the evolution of visual acuity. Since no further impact of time within the second year was observed, one set of transition probabilities could be generated for this second year to sufficiently mimic the actually observed VA level evolution. The purpose was to generate the minimally required set of transition probabilities over time, to be used in the model.

The aim of this method was to optimally mimic the clinical trial observations, for all levels of VA at treatment start, and to avoid the need for assumptions regarding the relative efficacy of treatment in relation to baseline VA level.

This model could thus predict the probability of being in a specific state (any of the 5) depending on the state of the previous quarter (any of the 5), which are thus the transition probabilities. These probabilities (and the 95% confidence intervals) were calculated using this model.

These models were created per type of patient and study based on data from the ANCHOR, MARINA, PIER, TAP studies for the following lesion types; minimally classic (MC), occult (OC) and predominantly classic (PC).

There were 5 states, scored 1 to 5. These scores correspond with following visual acuity scores: 1 = $\geq 20/50$; 2 = 20/60-20/100 ; 3 = .20/125-20/160 4 = 20/200-20/400; 5 = $< 20/400$.

Page 117, Data inputs, 3rd paragraph

This section states,

“Since the TAP study population included patients with all lesion types (predominantly, minimally classic and occult no classic) the comparability of patient populations in the data used for the indirect comparison would need to be established (specifically whether the efficacy of PDT was based on only the subgroup of patients with predominantly classic lesions in the TAP study) before generating efficacy estimates for the comparison of ranibizumab and best supportive care.”

The data derived from the TAP study for the purpose of indirect comparisons were derived separately and specifically for PC lesions, and applied in the model. In addition, the TAP visual acuity transition probabilities were included in the probability sensitivity analyses in the Novartis model.

Page 117, Data inputs, 4th paragraph

This section states, “The cost of concomitant therapy for the PDT cohort was included as part of the AMD treatment and yet a separate concomitant treatment was added when estimating the average total cost for each treatment cycle.”

After checking the model again we can confirm that there is a double counting error for the costs of concomitant medication associated with AMD treatment costs. These costs were initially included in AMD treatment costs but it was subsequently decided that a separate category should be added for concomitant medication. The AMD costs should have been amended accordingly but the correction was omitted in error. The sensitivity analysis conducted by the Assessment Group demonstrates that even when the double-counting errors are corrected the estimates of cost-effectiveness for all lesion types are still below £30,000. The corrected incremental cost-effectiveness ratios as presented on page 121 of the Assessment Report are as follows;

PC lesions vs PDT - £8,121/QALY,
PC lesions vs BSC - £15,322/QALY,

MC lesions vs BSC - £27,174/QALY and
OC lesions vs BSC - £27,767/QALY.

In summary, the Assessment Report and independent economic model confirm that ranibizumab is a clinically and cost effective therapy for the treatment of wet AMD. In addition, the recommended dose frequency means that ranibizumab is likely to prove even more cost-effective than the current Assessment Groups estimates suggest. The available evidence base fully supports the use of ranibizumab within its licensed indications for the treatment of wet AMD.