The Royal College of Ophthalmologists
17 Cornwall Terrace, London. NW1 4QW.
Telephone: [redacted]
Facsimile: [redacted]
Email: [redacted]
Website: WWW.RCOPHTH.AC.UK

PATRON HRH THE DUKE OF YORK, KG, KCVO, ADC

The Royal College of Ophthalmologists response to the NICE Appraisal Consultation Document

Ranibizumab for the treatment of macular oedema secondary to retinal vein occlusion

The Royal College of Ophthalmologists is disappointed with the Appraisal Committee's preliminary recommendations not to recommend ranibizumab intravitreal injection for the treatment of macular oedema following either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). The basis of this preliminary opinion is on cost effectiveness and differences between the manufacturer's modelling and the ERG assessment on several key parameters. Specific comments regarding the key assumptions/parameters are outlined below:

i. Use of "worse –seeing eye" rather than "better-seeing eye" in modelling

It is agreed that both in clinical practice and in the pivotal BRAVO and CRUISE trials that the majority of patients present with RVO in their worse seeing eye and that the ERG's assumption to model on this is appropriate. However, the committee has failed to make any specific recommendation on the cost effectiveness for those patients who do actually present with RVO in their better-seeing eye. This could be in up to 10% of cases or 3000 cases per annum in UK. It appears from Table 67 of the ERG report that if a patient does present with CRVO in their better-seeing eye then the use of ranibizumab in this particular cohort is highly cost effective at £9,515 ICER of ranibizumab versus best supportive care. This raises the sensitive ethical issue of whether it is appropriate to not treat a patient when it is their worse seeing eye affected whilst having a highly cost effective treatment if the better seeing is affected. This issue cannot be ignored and must be addressed in any Final Appraisal Document.

ii. Utility values used in model

There are significant uncertainties around the specific utility values used in the modelling. In section 4.15 of the ACD the committee states that they accepted the ERG's recommendations for the use of utility values from Brazier et al (2009) rather than the manufacture's submission of utility scores from Brown et al (1999) based on the need for age adjustment.
Further justification for this appears to be that Brazier et al (2009) utility scores assessment was recommended in NICE TA 155 for AMD and that it is generally accepted that it is the level of visual acuity rather than the particular visual disorder that drives the utility score. Although this latter point is accepted it must be pointed out that the Brazier et al paper (2009) used 108 general population volunteers with a mean age of 32 yrs wearing contact lenses to simulate AMD visual states for approx. 1.5 to 2 hours whilst utility scores were estimated through interview. This is in contrast to the Brown et al (1999) utility scores which were derived from 325 participants with visual disorders (7% had RVO) and a mean age of 67.5 years. It is recognised that reimbursement agencies around the world prefer general population values and that specific patient utility scores may differ from the general population. However, the stark differences in how the utility scores are calculated between these 2 studies raises the significant possibility that utility score benefit from ranibizumab in RVO is underestimated in this appraisal.
In section 4.2 the committee acknowledges that "loss of vision caused by macular oedema

secondary to retinal vein occlusion seriously impairs health-related quality of life" and yet the analyses used does not appear to appropriately reflect this sentiment.
In the ERG updated report and erratum the ERG state that " some simplifying assumptions were made surrounding the application of a smaller set of utility values to a larger number of health states; these assumptions are summarised in Table 54."
For better-seeing eye calculations it would appear that the way Brazier utility scores are implemented could underestimate potential benefit. For example, a gain from 56 letters to 75 letters (i.e. 19 letter gain) would not register as an improvement in utility score (a 10 letter gain is often considered clinically relevant and benefit)

Table 54. The implementation of utility values from Brazier *et al.*[40]

Visual acuity health state	Base case utility	Brazier utility
86–100 letters (20/16–20/10)	0.920	0.706
76–85 letters (20/32–20/20)	0.880	0.706
66–75 letters (20/64–20/40)	0.770	0.681
56–65 letters (20/80–20/50)	0.755	0.681
46–55 letters (20/125–20/80)	0.670	0.511

iii. Pooling/Unpooling of Transition probabilities

The ERG's assessment clearly demonstrate that the pooling or unpooling of transition probabilities has a substantial impact on the overall ICER for ranibizumab versus grid laser photocoagulation in BRVO (i.e. raising the ICER from £20,494 to £52,004 per QALY gained). The ERG report states "The ICER obtained for ranibizumab versus GLP (standard care) in MO secondary to BRVO rose to £52,004 in the first analysis and ranibizumab was dominated in the remaining analyses. This confirmed the supposition that this approach (of pooling transition probabilities) inflated the effect of ranibizumab. However, the impact of this approach on the effect of GLP remains unknown." Presumably, the unpooled transition probabilities in the Sham/0.5mg column of table 57 of the ERG report may over-estimate the effect of laser due to the concomitant use of ranibizumab over 7-12 mths in this arm. This aspect needs further clarification.

The ERG are concerned that the sham arm of BRAVO 0-6mths does not represent a true reflection of a GLP laser treated cohort as only 57.6% of patients in this arm actually received laser. In section 5.4.6 of the ERG report it is stated that " The use of GLP in the sham arm does not represent the use of GLP in clinical practice as all patients in the sham arm would have been eligible for GLP after having MO for 3 months". This not completely accurate and misleading.

In the BRAVO study it was at the clinician's discretion whether to treat with laser based on assessment as to whether haemorrhage had cleared sufficiently to allow safe laser treatment and certain anatomical and functional criteria were met. The criteria used in BRAVO is consistent with how patients would be treated in the NHS with the standard of care and thus the sham arm of BRAVO should be considered a true representation of standard of care in BRVO. As there is no true direct comparative study of ranibizumab versus laser it is noted that the ERG have attempted to do further indirect modelling of ranibizumab versus laser by using the sham

arm of the Moradian et al study. In the report the ERG state “The direction of bias in this analysis was likely to be towards ranibizumab and the result was an improvement of 8 letters for ranibizumab at month 3 compared with GLP.” It must be stated that although there is undoubtedly some improvement with time in GLP treated patients and that a 3 month timeline may not capture this the clinical experience of the benefit of using ranibizumab far exceeds any potential benefit seen in laser treated patients.

iv. ICER of Ranibizumab versus Dexamethasone Implant

It is agreed that the committee’s decision to consider an indirect comparison with dexamethasone intravitreal implant for CRVO and BRVO was acceptable. However, due to the significant difference in duration of macular oedema, presenting level of visual acuity and retinal thickness of the pivotal studies (BRAVO/CRUISE versus GENEVA) then any comparison must be considered with caution. The Committee conclude that these differences between the studies would bias ranibizumab and thus the ERG’s exploratory assessment of the ICERs for CRVO of £37,400 per QALY and £31,100 for BRVO are likely to be higher. However, it is not clear whether the ERG or the Committee have adequately taken into account the adverse event rate of cataract development of 30% and the raised intraocular pressure event rate requiring glaucoma topical medication of 25% in the dexamethasone treated group after just 2 injections. Presumably, if these adverse events rates are considered then the calculated ICERs may be lower and potentially bias against ranibizumab.

It must be stated that there are many patients who present with RVO but who have relative contra-indications to dexamethasone implant such as uncontrolled raised intraocular pressure (IOP) or past history of difficult to control IOP. In such patients then dexamethasone would not be considered best practice and the strong clinical evidence would be to recommend ranibizumab in preference to dexamethasone. A further group of patients that would be relatively contraindicated for dexamethasone implant are younger patients who would not normally be at risk of developing cataract but may have a 30% risk after only 2 implant injections over the period of 1 year.

v. Use of bevacizumab as a comparator

In section 4.7 the ACD states “The Committee noted that licensing is not a prerequisite for consideration of a comparator in a NICE technology appraisal as long as it is in routine use or is considered to be best practice.” It is important to state that the use of bevacizumab in RVO cannot be considered routine in the NHS and certainly not considered best practice as 2 licensed products are indicated in RCOphth Interim RVO guidelines (Dec 2010). Although many ophthalmologists throughout the UK have used bevacizumab in selected RVO cases, at present the majority of RVO patients do not receive anti-VEGF treatment, and the practice varies widely from unit to unit dependent on local NHS Trust pharmacy approvals. In addition there is significant variation in dosing schedules and no universally agreed treatment protocols. Although indirect comparisons can be made between ranibizumab and bevacizumab in RVO the analyses must be viewed with caution. The long-term benefit and need for repeated treatment for both ranibizumab and bevacizumab are unknown. The Royal College of Ophthalmologists has recently issued a statement (14th December 2011) regarding the use of anti-VEGF agents in the treatment of neovascular age-related macular degeneration (AMD) and is of the view that, in the case of neovascular AMD, the current published literature is consistent with the conclusion that bevacizumab and ranibizumab are equally effective and there is no convincing evidence of a clinically significant difference in the incidence of serious adverse events between the two groups. However, it remains unknown whether similar conclusions will be reached when studies comparing directly between the two agents in RVO are available. It is likely that between 5 and 9 repeated treatments with bevacizumab will be required over the first 12 months. The clinical effect of bevacizumab probably lasts for 6-12 weeks. Patients are likely

to need review 6-8 weekly over the first 12 months. The ancillary investigations for each of these visits such as vision assessment and OCT measurement are anticipated to be the same at each visit. It would be anticipated that the injection procedure and associated costs would be identical for ranibizumab and bevacizumab

In reply to specific questions the answers are outlined below:

Has all of the relevant evidence been taken into account?
All relevant evidence has been taken into account except for the 12month papers from BRAVO and CRUISE which give significant p values for the 12 month data :

Brown DM, Campochiaro PA, Bhisitkul RB, Ho AC, Gray S, Saroj N, Adamis AP, Rubio RG, Murahashi WY. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion:12-month outcomes of a phase III study. Ophthalmology. 2011 Aug;118(8):1594-602.

Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N, Murahashi WY, Rubio RG. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmology. 2011 Oct;118(10):2041-9.

In addition it is not clear whether the 12 month GENEVA data paper was used for AE rate in the comparison ICER calculations of ranibizumab versus dexamethasone :

Julia A. Haller, Francesco Bandello, Rubens Belfort Jr, Mark S. Blumenkranz, Mark Gillies, Jeffrey Heier, Anat Loewenstein, Young Hee Yoon, Jenny Jiao, Xiao-Yan Li, Scott M. Whitcup for the Ozurdex GENEVA Study Group. Dexamethasone Intravitreal Implant in Patients with Macular Edema Related to Branch or Central Retinal Vein Occlusion: Twelve-Month Study Results. Ophthalmology. 2011 Dec;118(12):2453-60

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Summary of clinical effectiveness is fair except that in section 4.5 of the ACD it states " It also noted that ranibizumab provided sustained gains in BCVA at 12 months in both BRAVO and CRUISE, but that these were not statistically significant." This is incorrect as stated above the p values in the papers cited above are highly significant for benefit in BRAVO and CRUISE at 12 months (p=<0.01 and p=<0.001 respectively).

There are particular concerns regarding interpretation of the evidence with regards to cost effectiveness as outlined in sections i) to v) above. The issue of better-seeing eye analysis versus worse-seeing eye seems appropriate but there are significant uncertainties regarding other key parameters such as source of utility scores used and ICER analysis of ranibizumab versus GLP.

The cost effectiveness if a patient presents with CRVO in their better-seeing eye (10% of patients) needs a clearer statement. It appears from Table 67 of the ERG report that if a patient does present with CRVO in their better-seeing eye then the use of ranibizumab in this particular cohort is highly cost effective at £9,515 ICER of ranibizumab versus best supportive care.
The ICER calculation for ranibizumab versus dexamethasone for both BRVO and CRVO appears to underestimate the cost of adverse events for dexamethasone implant. The cost of AEs for ranibizumab is calculated at £61.00 (see tables 69 and 74 of ERG report) whilst for dexamethasone implant is only £152.00 (see tables 72 and 75 of ERG report). It is not clear what rate of IOP medication or cataract rate is used for these analyses. Previously, the 6 month

cataract rate of 7.3% from the original Geneva trial has been used to estimate the extrapolated cataract rate at 12mths or after 2 injections. However, a recent update of the GENEVA trial shows that the cataract rate after 2 dexamethasone implant injections at 12 mths is as high as 29.8% (90/302 phakic eyes : Dexamethasone Intravitreal Implant in
Patients with Macular Edema Related to Branch or Central Retinal Vein Occlusion
Twelve-Month Study Results : Haller et al Ophthalmology. 2011 Dec;118(12):2453-60). It is possible that the cataract rate for repeated dexamethasone injections has been underestimated and that this could lead to an increased cost of AEs for dexamethasone and a subsequent reduction in the ICER.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
Further clarification over the issue of the cohort of patients presenting with RVO in their better-seeing eye and ICER calculations is required.

In the case of CRVO, the committee agree that "It was aware that current standard treatment in the UK (for CRVO) is dexamethasone or anti-VEGF drugs and therefore comparing ranibizumab with best supportive care in CRVO was not relevant to UK clinical practice." This is an appropriate statement and consistent with the RCOphth interim guidelines on RVO management (Dec 2010). Thus comparing ranibizumab with dexamethasone the committee state the most plausible ICER is £37,400 per QALY. The RCOphth are concerned that the AE cost for dexamethasone may have been underestimated and that the ICER value may be lower.
In the case of BRVO, the committee state that "… the most plausible ICER for ranibizumab versus dexamethasone in BRVO was £31,100 per QALY gained while ranibizumab versus grid laser photocoagulation in BRVO was likely to be in excess of £20,500 per QALY gained." As with CRVO there may have been an underestimate of the AE cost of dexamethasone.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?
No

Matters of factual nature
In section 3.5 the ACD states "…..At month 12 of the BRAVO trial (that is, at the end of the 6-month observation period, during which all patients could receive ranibizumab as needed), the 0.5 mg ranibizumab group reported an average gain in BCVA baseline score of 18.3 letters (95% CI 15.8 to 20.9) compared with the sham (plus ranibizumab) group that had gained 12.1 letters (95% CI 9.6 to 14.6, **p value not reported**)." The p value is reported in the full published paper as p = <0.01 (Brown DM, Campochiaro PA, Bhisitkul RB, Ho AC, Gray S, Saroj N, Adamis AP, Rubio RG, Murahashi WY. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion:12-month outcomes of a phase III study. Ophthalmology. 2011 Aug;118(8):1594-602.)

In section 3.6 the ACD states "… in the CRUISE trial … The manufacturer reported that the improvements in visual acuity in the ranibizumab group at month 6 were generally maintained, through to month 12 with treatment as needed (13.9 letters [95% CI 11.5 to 16.4] for ranibizumab; 7.3 letters [95% CI 4.5 to 10.0] for sham (plus ranibizumab) group; **p value not reported**)." The p value is reported in the full published paper as p = <0.001 (Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N, Murahashi WY, Rubio RG. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmology. 2011 Oct;118(10):2041-9.)

In section 4.5 the ACD states “It also noted that ranibizumab provided sustained gains in BCVA at 12 months in both BRAVO and CRUISE, but that these were not statistically significant.” This is incorrect as stated above the p values are highly significant for benefit in BRAVO and CRUISE at 12 months (p=<0.01 and p=<0.001 respectively).

In section 3.18 the ACD states “Furthermore, clinical advice to the ERG suggested that concomitant use of ranibizumab and grid laser photocoagulation does not represent how ranibizumab would be used in clinical practice.” It is likely that in the majority of patients ranibizumab would be used as monotherapy. However, there will be a proportion of patients who may be considered for combination therapy with laser. In the BRAVO study 21.4% of patients received concomitant laser in the initial 6 month treatment period of ranibizumab. This would be a reasonable estimate for practice in the NHS with the available evidence.

[redacted]

12th December 2011

On behalf of The Royal College of Ophthalmologists