Dear Sir / Madam,

I am writing on behalf of NHS Wirral as a consultee for the Appraisal Consultation Documentation (ACD) for macular oedema (retinal vein occlusion) – ranibizumab.

NHS Wirral agrees with the ACD that that ranibizumab should not be recommended for the treatment of visual impairment caused by macular oedema secondary to retinal vein occlusion. Wirral PCT does regard eye disease as an important area for commissioning and therefore would value innovative interventions for this disease if they were clearly cost effective and affordable. However, there are other treatment options that are available to treat this disease area which are considerable more cost effective.

Consideration of the clinical evidence

a) The trials were not comparable to clinical practice:

The two main trials that assessed ranibizumab for macular oedema secondary to retinal vein occlusion were CRUISE and BRAVO. Both of these trials excluded people with brisk afferent pupillary defect which is severe retinal ischaemia. There is therefore a lack of evidence for the effectiveness of ranibizumab for treatment of RVO in patients with severe ischaemia.

The outcomes in the trial of ranibizumab for branch retinal vein occlusion were confounded. In the BRAVO trial, patients were treated with monthly ranibizumab or sham injections for six months however, after three months the patients could receive grid laser photocoagulation for rescue treatment. This was used in 57.6% of patients in the sham injection group and 21.4% of the ranibizumab group in the first six months. It was noted that the treatment period of the BRAVO trial was insufficient to capture any benefits of grid laser photocoagulation on patient outcomes, which may last longer than three years. Clinical advice to the ERG suggested that concomitant use of ranibizumab and grid laser photocoagulation does not reflect how ranibizumab would be used in clinical practice and therefore, data from the BRAVO trial should be treated with caution.

b) The trials did not compare ranibizumab to currently used treatments:

Both trials had compared ranibizumab to sham injection rather than treatments used in current clinical practice (bevacizumab and dexamethasone invitreal implants). Although there were differences in the study populations of a study that had assessed dexamethasone (GENEVA), such as time to treatment after emergence of oedema, it was determined that indirect comparisons could be made.

The manufacturer did not compare ranibizumab with bevacizumab which was agreed to be an appropriate comparator in the scope. Bevacizumab (Avastin), like ranibizumab inhibits VEGF. It has marketing authorisation to be used in the treatment of some cancers, but has been used off-license for the treatment of macular oedema at lower doses.

Comments from clinical specialists were that ranibizumab had approximately equal effectiveness to bevacizumab but because a license has not been sought for the use of bevacizumab in the eye, its safety in the eye is not assured. Additionally concerns were raised from patient experts about the use of unlicensed treatments for which there was no post-marketing surveillance, particularly if there were licensed alternatives. The Committee said that “licensing is not considered a prerequisite for

consideration of a comparator in a NICE technology appraisal as long as it is in routine use or is considered best practice". Clinical specialists said that bevacizumab is currently reasonably widely used in the NHS, but the extent of its use varies between centres. All the clinical specialists involved said they used bevacizumab and NHS Wirral feels it is appropriate that it is considered a relevant comparator for ranibizumab. It is used on Wirral for the treatment of macular oedema secondary to retinal vein occlusion.

However, the ERG has carried out indirect comparisons with both bevacizumab and dexamethasone which were considered by the committee therefore, we are happy that all the relevant evidence has been taken into account.

For ranibizumab the Committee concluded that ranibizumab is one of a group of innovative anti-VEGF treatments, and does not stand alone in this therapeutic area and its benefits are appropriately captured in the QALY calculation**.** Ranibizumab does not offer patients enough benefits over current treatments at a cost effective price for the NHS. Bevacizumab is considered to have approximately equal effectiveness but at a considerably reduced cost compared to dexamethasone and dexamethasone offers the benefit of reduced dosing – every 6 month as opposed to potentially every month. This is both more appealing to patients who have fewer injections and also from the point of view of service delivery and capacity in the ophthalmology clinics.

Cost effectiveness

Ranibizumab for the treatment of macular oedema secondary to RVO is not a cost effective use of NHS resources and the Committee determined that the most plausible ICERs for ranibizumab compared with alternatives were all above the ranges usually considered cost-effective for NHS use (i.e. £20,000 to £30,000 per QALY gained).

For CRVO; Base case estimates produced by the ERG were an ICER of £43,800 per QALY gained for ranibizumab versus best supportive care, and £37,400 per QALY versus dexamethasone. The Committee agreed that ranibizumab and bevacizumab were approximately equally effective and the ERG performed an analysis that concludes "ranibizumab would need to generate 1.7 times more QALYs than bevacizumab (each month between months 2 and 6) in macular oedema secondary to CRVO to give an ICER at the top end of the range usually considered cost effective".

Bevacizumab was dominant over ranibizumab in a cost minimization analysis meaning that it is better value for the NHS.

Dexamethasone was considered an appropriate comparator as it is currently recommended for use in this indication in the NHS. The ICER for ranibizumab versus dexamethasone intravitreal implant in CRVO was estimated to be in excess of £37,400 per QALY gained.

For BRVO, the manufacturer's estimate of £20,500 per QALY gained for ranibizumab versus grid laser photocoagulation was thought to be an underestimation. The ICER for ranibizumab versus dexamethasone for people with BRVO was £31,122.

NHS Wirral are satisfied that there are no 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. Neither do we believe there are any equality -related issues that need special consideration that are not covered in the appraisal consultation document.

NHS Wirral feels strongly that the provisional recommendations in the ACD are sound and are a suitable basis for guidance to the NHS. Whilst ranibizumab is an effective treatment for macular oedema secondary to retinal vein occlusion there are other treatment options available to patients and the extremely high cost of ranibizumab compared to the other therapies means that it is just not a cost effective use of NHS resources.

Other services (especially eye services) may be withdrawn or stretched if the FAD were to change to recommending ranibizumab for this indication.

Yours Faithfully

[redacted]
On behalf of NHS Wirral