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FROM THE CHAIRMAN OF THE SCIENTIFIC COMMITTEE
MR. WINFRIED M. AMOAKU FRCS FRCOPHTH PHD

1st March 2011

Ms. Lori Farrar
Committee C Project Manager
NICE
Level 1A, City Tower
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Dear Ms. Farrar,

Re: Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion

The Appraisal Committee's preliminary recommendations state the Committee is minded not to recommend dexamethasone intravitreal implant 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 that the Committee requests further clarification from Allergan with regard to three main areas:

i. Clinical and cost effectiveness of dexamethasone intravitreal implant compared with bevacizumab

ii. A revised base case for the cost effectiveness of dexamethasone intravitreal implant incorporating several revised analysis points

iii. Further clarification of the location and extent of macular haemorrhage for the subgroup of patients for whom laser treatment was not considered appropriate because of macular haemorrhage.

In general terms, the request for these areas of clarification appears reasonable. These specific areas are discussed below.

i. Clinical and cost effectiveness of dexamethasone intravitreal implant compared with bevacizumab

It must be stated that the request for a submission from Allegan with regard to a comparison with bevacizumab was clearly outlined in the scope of the appraisal and identified in the ERG submission dated 01-12-2010. In the manufacturer's submission (section 5.7), Allergan state that no indirect comparison could be made with bevacizumab owing to absence of appropriate RCT evidence. The lack of comparator analysis has been influential in prompting the need for further clarification and subsequent delay and significant responsibility for this must lie with the manufacturer, if such data exists.

In section 4.5 of the ACD the document states that the Committee heard that Avastin is widely used in NHS clinical practice. However, it is important to state that this is not completely correct. Although many ophthalmologists throughout the UK use Avastin in selected RVO cases at present the majority of RVO patients do not receive anti-VEGF treatment, and that practice varies from unit to unit dependent on local NHS Trust pharmacy approvals, that there is significant variation in dosing schedules and no universally agreed treatment protocols as stated in the RCOphth original submission. Bevacizumab use in RVO could not be considered routine in the NHS.

Due to the lack of common agreed protocols for bevacizumab use in RVO any indirect comparison will be difficult. Although some case series have shown benefit in treatment of macula oedema in RVO there is a lack of RCT evidence of efficacy and safety. The long-term benefit and need for repeated treatment are unknown. 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 as for dexamethasone implant. In the majority of units the bevacizumab injection would be performed as an out-patient procedure as opposed to day cases injection of dexamethasone implant (although as stated by the clinical expert and referred to in the ACD – after a learning curve it is anticipated that the dexamethasone implant will be performed primarily as an out-patient procedure).

ii. A revised base case for the cost effectiveness of dexamethasone intravitreal implant incorporating several revised analysis points

The request for costs to be modelled on daycase dexamethasone implant is reasonable but it is anticipated that after a short learning curve most of the injections will be given as an out-patient procedure. The costs for visits noted by the manufacturer in their submission are outlined in table 108 and are based on a survey of 4 ophthalmologists in Scottish practice. The costs are broadly acceptable but are certainly less than the costings that are presently recommended by RCOphth for an AMD service (ref Commissioning Contemporary AMD Services: A guide for commissioners and clinicians July 2007 available at http://www.rcophth.ac.uk/page.asp?section=451&sectionTitle=Clinical+Guidelines).

Although there are obvious differences in provision of services for AMD and RVO, there are many similarities such as VA assessment, OCT assessment, ancillary drugs such as povidone iodine and antibiotics, staffing and administrative costs. There is also a significant discrepancy in Table 108 where the assessment of a BRVO pt is £150 (20%) cheaper than CRVO on the basis of 1 less indirect ophthalmoscopy assessment which seems unusual.

The request for “modelling of the fellow eye involvement, ensuring that costs of blindness are applied only to patients in whom both eyes fall into the worst health state is essential” is noted.

The RCOphth agree that manufacturer should have applied the cost savings associated with preventing severely impaired vision only when both eyes had visual acuity of less than 38 letters, as presented in the ERG's exploratory analyse, as this has a significant impact on cost savings.

The request for further modelling on retreatment rates is appropriate as in the manufacturer’s submission it is assumed that if the patient has no macular oedema at day 180 then they will require no further treatment. However, this does not reflect clinical practice as these patients may still require treatment at subsequent visits.

iii. Further clarification of the location and extent of macular haemorrhage for the subgroup of patients for whom laser treatment was not considered appropriate because of macular haemorrhage

As the manufacturer has not submitted modelling of dexamethasone implant against macular laser in non-ischaemic BRVO it is important to be clear that the extent of the macular haemorrhage in their treated group is such that no macular laser could be applied. This is a relatively subjective

decision as to whether laser therapy may have been appropriate but the request for clarification seems reasonable. Laser photocoagulation is avoided in the presence of significant macular haemorrhage.

The absence of a comparison of dexamethasone implant versus grid laser photocoagulation for non-ischaemic BRVO is an important omission. The RCOphth RVO Guidelines (December 2010) state in section 7.3.4.1.2

"If patients with macular oedema secondary to BRVO are seen within 3 months of onset of BRVO, consider pharmacotherapy with Ozurdex which is licensed or ranibizumab which is unlicensed but has robust clinical evidence of efficacy."

"If patients are seen after 3 months from onset of BRVO, consider laser photocoagulation or pharmacotherapy with Ozurdex which is licensed or ranibizumab which is unlicensed but has robust clinical evidence of efficacy."

In both these scenarios the clinician will be left with the dilemma as to whether dexamethasone implant should be funded and may lead to varying interpretations of whether a particular eye has sufficient haemorrhage to be considered as ineligible for macular laser. In the < 3months group there may be a perverse incentive to classify the macular haemorrhage as not amenable to laser therapy so as not to delay treatment.

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 omission of comparative data for bevacizumab and laser for macular oedema in BRVO as stated above. In addition, the costings for delivering an injection service should be considered from the RCOphth document "Commissioning Contemporary AMD Services: A guide for commissioners and clinicians July 2007" (available at http://www.rcophth.ac.uk/page.asp?section=451&sectionTitle=Clinical+Guidelines)

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
As stated above the concerns of the Committee with regard to cost effectiveness modelling are considered reasonable. It must be re-iterated that a gain of 10 letters is considered clinical significant by clinicians and patients alike.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
The provisional recommendations are suitable given the necessary clarifications and lack of comparator modelling. However, there is significant unmet need for RVO therapy and with proven clinical effectiveness the requirement for a swift assessment is imperative

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 4.24 the ACD states "There is a 1% risk of needing treatment for glaucoma when dexamethasone is used." This is more accurately referred to as 1% risk of requiring glaucoma surgery after 2 injections of dexamethasone implant.

It must be re-stated that

i. Existing clinical practice which is laser based is destructive. Ischaemic RVO is significant cause of visual morbidity

ii. Dexamethasone implant has proven efficacy as supported by data acquired through robust clinical trials

iii. Dexamethasone implant is the only licensed preparation for the management of retinal vein occlusions

iv. Efficacy and safety profile for dexamethasone is now well established in short to medium term.

With kind regards.

Yours sincerely,

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