NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

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

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Allergan Ltd UK	Further to the Appraisal Consultation Document issued 1st February 2011 Allergan submitted the following information: • A detailed response to the additional analyses requested by the NICE Appraisal Committee (core document and appendices) • A brief summary to address other detailed points highlighted within the Appraisal Consultation Document in response to the structured questions provided by NICE • A revised basecase economic model for OZURDEX (dexamethasone intravitreal implant) compared to standard of care (observation) • A new economic model providing an exploratory scenario analysis permitting comparison between OZURDEX (dexamethasone intravitreal implant) and anti-VEGF treatments occasionally used in NHS practice • Brief user notes to support ERG review of the 2 economic models provided	The Committee considered the additional information provided by Allergan. The additional evidence and the Committee's considerations of the additional evidence are summarised in the Final Appraisal Determination (sections 3.11-3.16, 4.12, and 4.15-4.24). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.
Allergan Ltd UK	Statement: Section 3.3, 4.21 – At day 180, there is no statistical significance between the sham and dexamethasone groups. Response: The clinical results discussed in section 3.3 only relate to one clinical measure of the efficacy of Ozurdex, specifically the proportion of patients achieving a ≥15 letter gain in BCVA in their study eye. Statistical significance was achieved for this measure at days 30, 60, and 90 and a similar trend was observed at day 180; however the window for scheduled post-implant visits varied, and many patients were assessed for efficacy considerably later than day 180 (197 patients treated with Ozurdex and 219 patients in the Sham group were assessed after day	Comment noted. The Committee reviewed all outcome data presented in the manufacturer's submission. However, section 3.3 refers specifically to the outcome of proportion of patients achieving at least a 15 letter gain (EMA endpoint). The NICE guidance document aims to briefly summarise the key evidence used by the Committee for decision making and it is not possible to present details of all outcomes collected in the trials at all time points. The manufacturer's additional submission and revised analyses submitted in response to the

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	180 of the ITT period). This is an important point, as we know from the pharmacokinetic profile of Ozurdex that after day 180 there are not therapeutic levels of dexamethasone in the eye. The exclusion of these patients in a post-hoc analysis resulted in a statistically significantly higher proportion of patients with an improvement of ≥ 15 letters BCVA at all time points, including day 180 (for 180 day visits up to and including day 180: 136-180), with Ozurdex (26%) versus Sham (17%) (P ≤ 0.017) (Figure 1). Figure 1: Effect of excluding visits beyond 180 days: BCVA improvement ≥15 letters – not presented here Additionally both individual and pooled data from the GENEVA studies demonstrated that the proportion of patients with an improvement in BCVA of ≥ 10-letters from baseline (a level which would be considered clinically significant) was statistically significantly higher at days 30, 60 and 90 (P ≤ 0.010); and additionally in GENEVA 009 and the pooled analysis at day 180 (P ≤ 0.037) with Ozurdex versus Sham (Table 1). Significant between-group differences in the pooled analysis were 26.2% [95% CI: 20.3%, 32.1%] at day 30, 25.0% [95% CI: 18.7%, 31.3%] at day 60, 15.2% [95% CI: 8.8%, 21.5%] at day 90, and 6.7% [95% CI: 0.4%, 13.0%] at day 180. Table 1: Proportion of patients with an improvement in BCVA of ≥ 10-letters from baseline (- 180 days) – not presented here	Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.
Allergan Ltd UK	Statement: 3.7 – Anterior chamber cells and retinal neovascularisation were also	Comment noted. The Committee reviewed all safety data presented in the manufacturer's

Consultee	Comment	Response
	reported Response: While this statement is correct, it does not provide information regarding the extent to which these adverse events are experienced by the Ozurdex and Sham groups. Additionally, there were statistically significant differences between the groups for both events; therefore, it is important to be accurately report the results for each treatment group. Anterior chamber cells occurred in <2% of the patient population with 5 (1.2%) of patients affected in the Ozurdex group vs. no occurrences in the Sham arm (p=0.031). Conversely, Retinal neovascularisation occurred more frequently in the Sham group than the Ozurdex group, 2.6% versus 0.7% (P = 0.032), respectively.	submission. The NICE guidance document aims to briefly summarise the key evidence used by the Committee for decision making and it is not possible to present details of all outcomes collected in the trials at all time points.
Allergan Ltd UK	Statement: 3.8 – Health effects were assumed to last 2.5 years in BRVO and 3 years in CRVO; thereafter, visual acuity was assumed to be stable. Response: The duration of treatment was assumed to be 2.5 years in BRVO and 3 years in CRVO. As stated above, it was assumed that visual acuity stabilised after this treatment period. However, as the health effects of treatment would be carried forward through the model (maintained as seen at the end of treatment) it is not accurate to state that health effects lasted only during the treatment period.	This has been changed in the Final Appraisal Determination (section 3.8).
Allergan Ltd UK	Statement: 3.14 – Although there was a statistically significant increase in BCVA based on the mean letter score with the dexamethasone implant, the ERG did not consider this to be clinically significant because most patients did not achieve a 15-letter improvement from baseline. Response: It is important to note that a 15 letter improvement in BCVA (measured by the ETDRS method) is a regulatory endpoint and the gold standard for assessing	The Committee considered the information provided by the manufacturer on the clinical effectiveness of dexamethasone which included data from the secondary endpoint (proportion of the population with a gain of 10 letters) and accepted that this was clinically significant (section 4.8 Final Appraisal Determination). However, section 3.3 refers specifically to the

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	treatments for registration purposes. A 15-letter change in BCVA using the ETDRS method considerably exceeds the amount required to have a high degree of certainty that the observed alteration is a valid change in VA and not attributable to random chance (Beck, 2007). The primary goal of treating BRVO and CRVO is to improve or prevent further loss of visual acuity (VA) and to reduce Macular Oedema (Hansen, 2007; Hoerauf,2007). In the GENEVA study, statistically significantly more Ozurdex patients achieved a ≥15 letter gain when compared to observation at all time points except day 180. Additionally, Ozurdex patients demonstrated significantly greater clinical effects in terms of mean change in BCVA and fewer patients losing letters of vision, as was described in the initial submission. Furthermore, the Appraisal Committee's clinical experts have stated that a 10 letter gain in BCVA would be considered clinically significant. Again, a statistically significantly greater proportion of Ozurdex patients achieved a 10 letter gain at all time points in the pooled analysis (Table 1). Based on the full body of evidence submitted to the ERG and evaluated by the Appraisal Committee we do not consider it the statement shown above to be accurate.	outcome of proportion of patients achieving at least a 15 letter gain (EMA endpoint). The NICE guidance document aims to briefly summarise the key evidence used by the Committee for decision making and it is not possible to present details of all outcomes collected in the trials at all time points.
Allergan Ltd UK	Statement: 3.15 – The ERG also expressed concern over the size of implantation needle which is larger than those for other treatment. [Commercial in confidence information removed.]	The additional information provided by the manufacturer in response to the Appraisal Consultation Document was reviewed by the Committee and the considerations of the Committee regarding adverse events are described in section 4.10 and 4.13 of the Final Appraisal Determination.
Allergan Ltd UK	Statement: 3.21; 4.31, p37 – The ERG and Appraisal Committee question the use of 6-12 month data and 3-6 month data to calculate transition probabilities for	The Considerations of the Committee regarding the use of 3-6 month RCT observation data are described in section 4.18 of the Final Appraisal

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	patients in the Ozurdex and observation after 1 year of treatment. This is explored thoroughly in the detailed submission provided in response to analyses requested in the Appraisal Consultation Document.	Determination.
Allergan Ltd UK	Statement: 4.5; 4.11 – Bevacizumab is widely used in the NHS This is explored thoroughly in the detailed submission provided in response to analyses requested in the Appraisal Consultation Document. a formal survey commissioned from the School or Health and Related Research at the University of Sheffield (ScHARR) suggests that the majority of centres surveyed regard bevacizumab as an occasional or exceptional treatment for this condition. In the majority of cases, individual funding requests are sent to primary care trusts for exceptional approval in order to fund the use of bevacizumab in this indication. This is in accordance with guidelines provided by the Royal College of Ophthalmologists (RCO) and guidance provided by the MHRA on the unlicensed nature of bevacizumab when used in the eye.	The Considerations of the Committee regarding the use of bevacizumab in clinical practice in the UK and its suitability as a comparator are described in section 4.5 of the Final Appraisal Determination. The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.
Allergan Ltd UK	Statement: 4.7 – The ERG had identified a number of clinical trials evaluating the effectiveness of bevacizumab and an indirect comparison could have been performed. This is explored thoroughly in the detailed submission provided in response to analyses requested in the Appraisal Consultation Document. In summary, in addressing the appraisal committee's questions around bevacizumab, it is important to recognise that the absence of robust controlled trials to quantify the efficacy and safety of bevacizumab in this indication hamper attempts to conduct a rigorous comparative analysis by usual means which would be considered scientifically valid.	The additional information provided by the manufacturer in response to the Appraisal Consultation Document and the considerations of the Committee regarding the evidence for the clinical effectiveness of dexamethasone compared with bevacizumab are described in section 3.7 and 4.12 of the Final Appraisal Determination. The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.

Consultee	Comment	Response
	Therefore, it has been necessary to use exploratory techniques to i) illustrate the feasibility of a network model approach to effect a mixed treatment comparison ii) consider a cost minimisation evaluation of OZURDEX relative to bevacizumab and iii) use data from another anti-VEGF (ranibizumab) to provide a proxy of the "best" possible efficacy and safety profile anticipated for bevacizumab	
Allergan Ltd UK	Are the provisional recommendations sound and suitable basis for guidance to the NHS? The Appraisal Committee have requested additional information to inform a final recommendation regarding the use of OZURDEX (dexamethasone intravitreal implant) within the UK NHS. Allergan have made every attempt to provide detailed analyses to support a final decision that will enable patients to have access to the first licensed treatment for macular oedema following retinal vein occlusion. Allergan believe that OZURDEX represents a significant advance for the preservation and improvement of vision in patients with macular oedema following RVO. The analyses provided demonstrate that OZURDEX is a cost (and capacity) saving strategy compared to the experimental use of anti-VEGF treatments in UK practice, and is cost effective compared to standard of care (observation). Are there any aspects of the ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? No	Comment noted. The Committee recognised the difficulties with the evidence base for bevacizumab and commended Allergan's attempts to provide a comparison of the relative clinical and cost effectiveness of dexamethasone and bevacizumab in response to the Appraisal Consultation Document

Consultee	Comment	Response
Royal College of Nursing	The Royal College of Nursing welcomes the opportunity to review this document. We note that 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). We note that the Committee recommended that NICE requests further clarification from the manufacturer on the use of this technology and that the information should be made available for the next Appraisal Committee meeting. There are no comments to make at this stage on behalf of the Royal College of Nursing. We look forward to receiving the outcome of the committee's further deliberation on this matter.	Comment noted.
Royal National Institute of Blind People/ Macular Disease Society	RNIB/MDS comments on the ACD for the appraisal of dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion 1. As a general comment we would like to express our appreciation for the fact that the ACD makes it clear where patient expert input has been considered by the Appraisal Committee and what conclusions it has drawn from this input. This makes it easier for us as patient organisations to justify the considerable time and resources spent on participating in the health technology appraisal process.	Comment noted.
Royal National Institute of Blind People/ Macular Disease Society	2. Our response to this particular ACD focuses on three issues: a. Use of bevacizumab as comparator b. The Appraisal Committee's draft recommendation c. The option of departing from the threshold	See responses below.
Royal National Institute of Blind People/ Macular	**Use of bevacizumab as comparator** The ACD is requesting from the manufacturer an analysis of the clinical and cost	The Committee considered the additional information provided in comments arising from the consultation on the Appraisal Consultation Document with regard to the use of bevacizumab in

Consultee	Comment	Response
Disease Society	effectiveness of dexamethasone intravitreal implant compared with bevacizumab including a cost-effectiveness analysis with varying vial sharing assumptions for treatment with bevacizumab We believe that this decision is not based on a reasonable interpretation of the evidence. We cannot recall the clinical specialists stating that bevacizumab is currently "widely used in the NHS" for this condition (see point 4.5). More importantly, no evidence has been provided for its routine use. The STA methods guide states that “relevant comparators are identified, with consideration given specifically to routine and best practice in the NHS (including existing NICE guidance) and to the natural history of the condition without suitable treatment. There will often be more than one relevant comparator technology because routine practice may vary across the NHS and because best alternative care may differ from routine NHS practice. For example this may occur when new technologies are used inconsistently across the NHS. Relevant comparator technologies may also include those that do not have a marketing authorisation (or CE mark for medical devices) for the indication defined in the scope but that are used routinely for the indication in the NHS. Comparator technologies may include branded and non-proprietary (generic) drugs. Sometimes both technology and comparator form part of a treatment sequence, in which case the appraisal may need to compare alternative treatment sequences. The scoping process aims to specify the comparator technologies as precisely as the technology under appraisal. Evidence providers will need to give due regard to all the above considerations when selecting comparator technologies for analyses in the evidence submissions.” We would argue that bevacizumab constitutes neither routine nor best practice (as	the treatment of macular oedema following retinal vein occlusion. The Considerations of the Committee regarding the use of bevacizumab in clinical practice in the UK and its suitability as a comparator are described in section 4.5 of the Final Appraisal Determination. The NICE guide for the Methods of Technology Appraisal 2.2.4 states that ‘relevant comparators are identified, with consideration given to routine and best practice in the NHS (including existing NICE guidance) and to the natural history of the condition without suitable treatment’ (emphasis added), and continues to describe that ‘there will often be more than one relevant comparator technology because routine practice may vary across the NHS and because best alternative care may differ from routine practice’.

Consultee	Comment	Response
	defined by the Royal College of Ophthalmologists) and that the Committee should provide evidence to the contrary before requesting the use of bevacizumab as a comparator in this appraisal. While there is evidence for routine use of bevacizumab in wet age-related macular degeneration we do not believe that there is sufficient evidence for its routine use in retinal vein occlusion. We would like to make it clear at this stage that we will consider appealing against the final NICE decision in this appraisal to ensure that the definition of comparators is clarified. The ACD talks about widespread use (point 4.7) and the fact that a comparator should be 'current or best practice in the NHS' (point 4.25) when in fact the test is whether it is in routine use and best practice.	
Royal National Institute of Blind People/ Macular Disease Society	Furthermore, we are concerned that the committee has not fully considered the available evidence for the effectiveness and safety of bevacizumab. The ACD stated that the ERG and the Royal College of Ophthalmologists "had identified prospective and retrospective studies and case series for bevacizumab in the treatment of macular oedema secondary to RVO (point 4.25). By contrast point 3.22 states that both "RCT and non-RCT evidence was available and could have been used in an indirect comparison". It is clearly important to ensure that the Committee has a clear understanding of the level of evidence available for the use of bevacizumab in RVO. From the above it appears that the reference to RCT evidence may be in relation to the use of bevacizumab in wet AMD rather than RVO. It would help to have this clarified since the evidence for the effectiveness and safety of bevacizumab in RVO is of a significantly lower level. Since no large RCTs have been conducted on the use of bevacizumab in RVO we	The additional information provided by the manufacturer and the considerations of the Committee regarding the evidence for the clinical effectiveness of dexamethasone compared with bevacizumab are described in section 3.7 and 4.12-4.13 of the Final Appraisal Determination. The NICE guide for the Methods of Technology Appraisal 5.3.4 states that non-randomised studies may be required to supplement RCT data. The Committee recognised the difficulties with the evidence base for bevacizumab and commended Allergan's attempts to provide a comparison of the relative clinical and cost effectiveness of dexamethasone and bevacizumab in response to the Appraisal Consultation Document

Consultee	Comment	Response
	would argue that a full cost-effectiveness analysis is methodologically unsound.	
Royal National Institute of Blind People/ Macular Disease Society	This combined with insufficient evidence of the routine use of bevacizumab for the treatment of macular oedema secondary to RVO in the NHS should lead the Committee to abandon bevacizumab as a comparator. This would seem the right decision to us, particularly given the failure to include ranibizumab as a comparator which is also not in routine use in the NHS but has a significantly better evidence-base for its effectiveness.	The Considerations of the Committee regarding the use of bevacizumab in clinical practice in the UK and its suitability as a comparator are described in section 4.5 of the Final Appraisal Determination. The Committee's conclusions about the cost effectiveness of dexamethasone compared with bevacizumab are described in section 4.23 and 4.24 of the Final Appraisal Determination.
Royal National Institute of Blind People/ Macular Disease Society	Finally, we would like to alert the Committee to the impact a cost-effectiveness analysis including bevacizumab is likely to have on patient access to treatment. Even though estimates of the costs of providing bevacizumab for the treatment of any eye condition vary widely and fail to include the costs of pharmacovigilence to ensure patient safety, we acknowledge that dexamethasone intravitreal implant is unlikely to be shown to be cost-effective if compared to bevacizumab. While the result of this cannot be a NICE recommendation to use bevacizumab in the NHS there appears to be an assumption that not recommending dexamethasone intravitreal implant for use in the NHS will lead to the cheaper, unlicensed alternative being made available routinely. We believe that this is misguided. Instead patients are likely to be denied access to any treatment as PCTs are under pressure to cut costs and the result will be avoidable blindness, particularly in people with CRVO who have no other treatment alternatives.	Comment noted.
Royal National Institute of Blind	**The Appraisal Committee's draft recommendation**	Comment noted.

Consultee	Comment	Response
People/ Macular Disease Society	We understand that the methods guide for technology appraisals requires the Appraisal Committee to issue draft recommendations in relation to the technology under consideration. However, we feel that it is not sufficiently clear why the Appraisal Committee has stated that it is minded not to recommend dexamethasone implant for the treatment of RVO given that it appears to have accepted key assumptions in the manufacturer's model (e.g. the '90:10 worse v better seeing eye' split, the need to treat first eyes, the relevance of 10 letter gains). All of these contribute to the large number of ICERs below the £30,000 threshold. In fact at present there is only one of the alternative scenarios (point 3.20) that yielded an ICER of more than £30,000. It would be helpful to have a clear explanation of the Committee's reasoning, i.e. that it made assumptions about the outcome of the additional analyses and the comparison with bevacizumab requested from the manufacturer or that the lack of data about the safety of earlier and more frequent retreatment are sufficient to decide against approval.	In Section 4.20 of the Final Appraisal Determination, the Committee concluded that the decision regarding the cost effectiveness of dexamethasone compared with best supportive care should be based on the manufacturer's ICER of £26,300 per QALY gained for all people with RVO. The Committee further concluded that this represented an acceptable level of cost effectiveness in this case and that dexamethasone intravitreal implant for the treatment of RVO represents a cost-effective use of NHS resources when compared with best supportive care.
Royal National Institute of Blind People/ Macular Disease Society	**Departing from the threshold** We would like to remind the Committee of the Citizens Council's report departing from the threshold includes references to the treatment of first or second eyes: "There was little doubt that most of us on the Council felt that the macular degeneration decision was most definitely an instance in which pure cost-effectiveness should have been put to one side. "Inhumane" and "shameful" were just two of the words that members used to describe it." We are pleased to see that the Committee came to the conclusion that "it was appropriate to treat the first eye affected" (point 4.15) and would like to see this reflected in the consideration of cost-effectiveness in case the additional cost-effectiveness analysis requested from the	In Section 4.20 of the Final Appraisal Determination, the Committee concluded that the decision regarding the cost effectiveness of dexamethasone compared with best supportive care should be based on the manufacturer's ICER of £26,300 per QALY gained for all people with RVO. The Committee further concluded that this represented an acceptable level of cost effectiveness in this case and that dexamethasone intravitreal implant for the treatment of RVO represents a cost-effective use of NHS resources when compared with best supportive care.

Consultee	Comment	Response
	manufacturer results in more ICERs above the £30,000 threshold.	
Royal College of Opthalmologists	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.	See responses below.
Royal College of Opthalmologists	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	The Committee considered the additional information provided in comments arising from the consultation on the Appraisal Consultation Document with regard to the use of bevacizumab in the treatment of macular oedema following retinal vein occlusion. The Considerations of the Committee regarding the use of bevacizumab in clinical practice in the UK and its suitability as a comparator are described in section 4.5 of the Final Appraisal Determination.

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	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).	The additional information provided by the manufacturer and the considerations of the Committee regarding the evidence for the clinical effectiveness of dexamethasone compared with bevacizumab are described in section 3.7 and 4.14 of the Final Appraisal Determination. The NICE guide for the Methods of Technology Appraisal 5.3.4 states that non-randomised studies may be required to supplement RCT data. The Committee accepted that there was uncertainty around the cost assumptions used in the cost minimisation comparing dexamethasone with bevacizumab.

Consultee	Comment	Response
Royal College of Opthalmologists	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	The additional information provided by the manufacturer and the considerations of the Committee regarding the evidence for the cost effectiveness of dexamethasone compared with observation are described in section 3.27, 3.28 and 4.15 to 4.20 of the Final Appraisal Determination. The additional information provided by the manufacturer and the considerations of the Committee regarding the additional scenario analyses for the cost effectiveness of dexamethasone compared with observation are described in section 3.13 and 4.19 of the Final Appraisal Determination. The Committee accepted that there was uncertainty around the cost assumptions used in the cost minimisation comparing dexamethasone with bevacizumab (section 4.21 to 4.24 of the Final Appraisal Determination).

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	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.	
Royal College of Opthalmologists	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	The additional information provided by the manufacturer and the considerations of the Committee regarding the additional information on macular haemorrhage are described in section 3.16 and 4.6 of the Final Appraisal Determination.

Consultee	Comment	Response
	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.	
Royal College of Opthalmologists	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)	The additional information provided by the manufacturer and the considerations of the Committee regarding the comparators are described in section 4.3-4.6 of the Final Appraisal Determination.
Royal College of Opthalmologists	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.	The Committee considered the information provided by the manufacturer on the clinical effectiveness of dexamethasone which included data from the secondary endpoint (proportion of the population with a gain of 10 letters) and accepted that this was clinically significant. However, the EMA endpoint for the trial was a gain of at least 15 letters and, therefore this evidence was presented in the Final Appraisal Determination. Section 3.3 refers specifically to the outcome of proportion of patients achieving at least a 15 letter gain (EMA endpoint). Section 4.8 acknowledges that the Committee heard that a gain of 10 letters is considered clinically significant. The NICE guidance document aims to briefly summarise the key evidence used by the Committee for decision making and it is not possible to present details of all outcomes collected in the trials at all time points.

Consultee	Comment	Response
Royal College of Opthalmologists	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	The considerations of the Committee regarding the clinical need of people with macular oedema following retinal vein occlusion are described in section 4.2 of the Final Appraisal Determination.
Royal College of Opthalmologists	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	Comment noted
Royal College of Opthalmologists	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.	This is no longer in the Final Appraisal Determination (section 4.24).
Royal College of Opthalmologists	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.	Please see previous responses for each individual point.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
None submitted		

Comments received from commentators

Commentator	Comment	Response
Commissioning Support Appraisals Service / NHS Waltham Forest	On behalf of the NHS Waltham Forest, I would like to submit our comments on the interim appraisal consultation document for Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion in the NHS. Based on the evidence considered, NHS Waltham Forest, is in agreement with the appraisal committee's decision and that this technology does represent a cost effective use of scarce NHS resources at present. • Dexamethasone has been compared against sham treatment in two phase III studies and demonstrated modest benefits in rate of improvement in visual acuity (15 or more letter improvement in best-corrected visual acuity (BCVA)). It is not clear whether there is a benefit compared to current treatment with intravitreal bevacizumab. • There were no between group differences in the proportion achieving response at 180 days although more improved with dexamethasone between days 30 to 90. • Dexamethasone increased adverse events. The Committee concluded that there were some concerns about the safety profile of dexamethasone treatment (given that the marketing authorisation is based on two re-treatments but the manufacturer assumed that up to six treatments would be given). The number of re-treatments required in practice remains unknown. During the trials, patients received	Comments noted. The additional information provided by the manufacturer and the considerations of the Committee regarding the clinical effectiveness of dexamethasone are described in section 3.7 and 4.14 of the Final Appraisal Determination. The additional information provided by the manufacturer and the considerations of the Committee regarding adverse events are described in section 4.10 and 4.13 of the Final Appraisal Determination.

Commentator	Comment	Response
	only two injections of dexamethasone and in the cost-effectiveness models. Re-treatment was assumed to occur at 6-monthly intervals with a maximum of five injections for BRVO and six injections for CRVO. The impact of more than two injections on adverse events is unclear; dexamethasone is delivered with a larger implantation needle than needed for other treatments. • Unit costs: The ERG suggested that administration of dexamethasone could be done on an outpatient basis (£150 per administration) and the unit cost of the implant is £870, a total of £1020. • Demand for treatment: The manufacturer estimates that approximately 23,000 new patients each year will be eligible for treatment in England and Wales. This estimate accounts for the proportion of people with RVO who would go on to develop macular oedema and then the proportion who would be eligible for dexamethasone treatment. This is approximately 126 new patients per 300,000 population per year. Based on this figure, total annual acquisition and implant costs for an average PCT (not including costs of adverse events) would be £128,520 (126 x £1050). • Comparator: The manufacturer restricted the comparator to observation, arguing that there are no other licensed comparators for this condition and that laser treatment was not appropriate for the subgroups under consideration in their decision problem. The ERG concluded that while it is true that there are no other licensed treatments, the use of bevacizumab is common under the 'specials' regime and there is evidence from case series of bevacizumab for this indication that could have informed the question through an indirect comparison.	The additional information provided by the manufacturer and the considerations of the Committee regarding costs are described in section 4.16-4.17 of the Final Appraisal Determination. The NICE Appraisal Committee does not consider budget impact in its decision making process. The considerations of the Committee regarding bevacizumab as a comparator are described in section 4.5 of the Final Appraisal Determination. The NICE guide for the Methods of Technology Appraisal 2.2.4 states that 'relevant comparators are identified, with consideration given to routine and best practice in the NHS (including existing NICE guidance) and to the natural history of the condition without suitable treatment' (emphasis added), and continues to describe that 'there will often be more than one relevant comparator technology because routine practice may vary across the NHS and because best alternative care

Commentator	Comment	Response
		may differ from routine practice'.
Commissioning Support Appraisals Service/NHS Birmingham East and North	RE: Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion On behalf of the Commissioning Support, Appraisals Service (CSAS), Solutions for Public Health, I would like to submit our comments on the interim appraisal consultation document for Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion in the NHS. Based on the evidence considered, CSAS is in agreement with the appraisal committee's decision and that this technology does represent a cost effective use of scarce NHS resources at present. • Dexamethasone has been compared against sham treatment in two phase III studies and demonstrated modest benefits in rate of improvement in visual acuity (15 or more letter improvement in best-corrected visual acuity (BCVA)). It is not clear whether there is a benefit compared to current treatment with intravitreal bevacizumab. • There were no between group differences in the proportion achieving response at 180 days although more improved with dexamethasone between days 30 to 90. • Dexamethasone increased adverse events. The Committee concluded that there were some concerns about the safety profile of dexamethasone treatment (given that the marketing authorisation is based on two re-treatments but the manufacturer assumed that up to six treatments would be given). The number of re-treatments required in practice remains unknown. During the trials, patients received only two injections of dexamethasone and in the cost-effectiveness models. Re-treatment was assumed to occur at 6-monthly intervals with a maximum of five	See response above to NHS Waltham Forest

Commentator	Comment	Response
	injections for BRVO and six injections for CRVO. The impact of more than two injections on adverse events is unclear; dexamethasone is delivered with a larger implantation needle than needed for other treatments. • Unit costs: The ERG suggested that administration of dexamethasone could be done on an outpatient basis (£150 per administration) and the unit cost of the implant is £870, a total of £1020. • Demand for treatment: The manufacturer estimates that approximately 23,000 new patients each year will be eligible for treatment in England and Wales. This estimate accounts for the proportion of people with RVO who would go on to develop macular oedema and then the proportion who would be eligible for dexamethasone treatment. This is approximately 126 new patients per 300,000 population per year. Based on this figure, total annual acquisition and implant costs for an average PCT (not including costs of adverse events) would be £128,520 (126 x £1050). • Comparator: The manufacturer restricted the comparator to observation, arguing that there are no other licensed comparators for this condition and that laser treatment was not appropriate for the subgroups under consideration in their decision problem. The ERG concluded that while it is true that there are no other licensed treatments, the use of bevacizumab is common under the 'specials' regime and there is evidence from case series of bevacizumab for this indication that could have informed the question through an indirect comparison.	

No comments:
Department of Health
Welsh Assembly Government

Comments received from members of the public

Role*	Section	Comment	Response
Commissioning Support Appraisals Service	NA	NHS Bradford and Airedale fully endorses the NICE position of not recommending dexamethasone for the treatment of macular oedema following retinal vein occlusion. The lack of an appropriate comparator group makes it difficult to assess both clinical and cost effectiveness. Furthermore, there are clear concerns over the adverse effects of dexamethasone that requires further attention. We endorse the NICE view of seeking evidence of the clinical and cost effectiveness of dexamethasone compared with bevacizumab, however, we would ask that NICE be mindful of the fact that Lucentis is being licensed for an increasing number of indications. It is well documented that the NHS is facing significant financial challenges, with little growth in budgets. If the NICE decision on dexamethasone were to be reversed, this would result in an increase in spend in the programme budget category of vision. Accordingly, in order to be able to fund dexamethasone, there will need to be disinvestment from existing services. If NICE were to reverse their decision there would need to be robust evidence of cost effectiveness. Because many PCTs will need to disinvest in other areas in order to fund dexamethasone, there is a risk that clinically and cost effective interventions and treatments may need to be disinvested in in order to fund dexamethasone. It is not clear if this treatment would be carried out in an inpatient or	Comment noted. Ranibizumab was not a comparator in the scope of this appraisal. The considerations of the Committee regarding the evidence base are described in section 4.24 of the Final Appraisal Determination.

Role*	Section	Comment	Response
		outpatient setting – if dexamethsone were to be approved for use, then commissioners would need to be very clear that this would be as an outpatient procedure.	
NHS Wirral		In response to the comment 'NICE is minded not to recommend this therapy': A joint application between primary and secondary care is about to be submitted to the Wirral Drug and Therapeutics Committee for the use of dexamethasone for the treatment of macular oedema following BRVO or CRVO. The basis of this application is for its use if laser therapy is unsuitable and instead of unlicensed triamcinolone or bevacizumab. With only two treatments per year, this would be much more acceptable for patients and there would be significant savings in theatre costs. On Wirral, we would prefer this treatment to be approved by NICE. The cost of using it is comparable with bevacizumab and much cheaper than ranibizumab, if this were licensed for the same indication. The ophthalmologists at the Wirral University Teaching Hospitals believe Ozurdex to be a good option for treating these patients. The proposed service builds upon existing capacity, infrastructure and personnel support.	The conclusion of the Committee regarding the evidence base is described in section 4.24 of the Final Appraisal Determination. Ranibizumab was not a comparator in the scope of this appraisal.

Role*	Section	Comment	Response
NHS Professional	1	The recommendation to compare against bevacizumab which is not licenced and therefore unlikely to be acceptable to all commissioners is inconsistent with the argument that comparison with ranibizumab is not recommended because it is not licensed for this indication. Ranibizumab is now licensed for diabetic macular oedema (6.1.2011) and if a direct comparison rather than a sham comparison is sought it should be with a licensed product.	Ranibizumab was not a comparator in the scope of this appraisal. The NICE guide for the Methods of Technology Appraisal 2.2.4 states that 'relevant comparators are identified, with consideration given to routine and best practice in the NHS (including existing NICE guidance) and to the natural history of the condition without suitable treatment' (emphasis added), and continues to describe that 'there will often be more than one relevant comparator technology because routine practice may vary across the NHS and because best alternative care may differ from routine practice'.
NHS Professional	2	It is important from the point of view of the patient to consider options for treatment that may offer less frequent interventions i.e. every 6 months as opposed to every 2 months. The reduced number of interventions will also have a positive impact on the commissioning of services as well.	Comment noted. The impact of dexamethasone on patients and the average number of doses with bevacizumab is considered in section 4.7 and 4.22 of the Final Appraisal Determination.