NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Dexamethasone intravitreal implant for treating diabetic macular oedema

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: IAN PEARCE, CONSULTANT OPHTHALMOLOGIST

Name of your organisation: St Paul's Eye Unit, Royal Liverpool University Hospital (Nominated clinical expert for Royal College of Ophthalmologists
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? NO
- other? (please specify)

What is the expected place of the technology in current practice?

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How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Centre involving Diabetic Macular Oedema (DMO) has a prevalence between 2-4% of diabetic pts. For the past 3 decades the standard of care has been with laser therapy to the macula delivered either in a grid pattern or focally to microaneurysms or with a combination of both. Although this approach reduced the progression of moderate visual loss (3 ETDRS lines of vision) from 24% to 12% there were only a limited number of cases that had improved visual acuity. Recently phase III trials have demonstrated the benefit of anti-VEGF treatment in the form of ranibizumab and more recently aflibercept. In particular, there has been up to 40% of cases gaining significant vision.This has led to a significant change in treatment for DMO. Non centre involving DMO is either observed (if visual acuity not affected and thickening >500um from the fovea) or treated with laser if oedema or exudates are threatening the central fovea area. In contrast centre involving DMO is more commonly associated with visual loss and best evidence supports the use of anti-VEGF treatment for these cases. The exact role of adjunctive laser in these cases is still debated but is still considered by many to have an adjunctive role and is still commonly performed in the UK. Ranibizumab is supported by NICE TA274 if there is central retinal thickness >400um. Since this TA247 guidance there has been widespread adoption of ranibizumab for this indication in DMO management. However, ranibizumab treatment involves regular monthly monitoring and injections. Most cases in the UK are managed with an initial 3 month loading phase followed by monthly monitoring with PRN treatment. The pivotal RESTORE trial using this regime suggest approximately 7-8 injections were need in the first year, 4 in the second year and 3 in the third year. Although this has transformed care for DMO patients the frequency of visits and injections has led different units to adopt different strategies including fixed regular dosing, extended PRN and Treat and Extend regimes. There is no

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For patients who are pseudophakic with chronic DMO with a sub-optimal response to previous anti-VEGF therapy then intravitreal fluocinolone implant is used as recommended by NICE TA301. For patients with DMO and evidence of vitreomacular traction then vitrectomy surgery is used (<7% of cases)

The introduction of intravitreal dexamethasone implant would be widely welcomed as an addition to the available therapies to treat DMO. It has been widely adopted as a therapy for retinal vein occlusion (RVO) following NICE TA229 and there is wide experience with its use for RVO. It would be delivered in a secondary care setting and expertise already is in place for its use.

The Royal College of Ophthalmologists have published comprehensive guidelines for the management of Diabetic Retinopathy.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

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The introduction of intravitreal dexamethasone implant would be widely welcomed as an addition to the available therapies to treat DMO. It has been widely adopted as a therapy for retinal vein occlusion (RVO) following NICE TA229 and there is extensive experience with its use for RVO. It is likely that there would be widespread adoption of the technology by ophthalmologists as an alternative to anti-VEGF sub-optimal responders or to reduce the frequency of monitoring visits and / or injection visits. It is difficult to predict whether it would be considered as first line along with anti-VEGF for DMO or whether it would be reserved as a second line agent for patients requiring regular monitoring / injections with anti-VEGF or sub-optimal responders. Experience with RVO would suggest that a proportion of ophthalmologists would consider it as an alternative firstline treatment along with anti-VEGF (supported by phase III data).
Although phase III studies were designed with the intravitreal dexamethasone to have a therapeutic window of upto 6 months the data form the phase III trials and real world experience with RVO would suggest that it does not have significant effect for that duration and it is more likely that it would repeated at between 4 and 5 months.
If no benefit is witnessed after a single injection in terms of reduced central retinal thickness or visual acuity improvement it is unlikely to be repeated. Due to the risk of increased intraocular pressure (IOP) It is likely to be avoided in patients with advanced glaucoma, difficult to control glaucoma/ocular hypertension (ie 2 or more medications). Due to the risk of cataract it is likely to reserved as a second line therapy in younger patients who do not have cataract and still have the ability for normal focussing for reading (ie not yet presbyopic – this is because the increased risk of cataract surgery which is often avoided due to the immediate effect on near focussing.)

The trial data to date reflects patients likely to be treated in the UK. It is likely, as stated above, if poor response in terms of reduced central retinal thickness or visual acuity after a single injection then it is unlikely to be repeated – unless there was an alternative cause for reduced acuity such as cataract. Likewise it is highly likely that if a good response is achieved it is likely that the implant injection would be repeated at 4-5 months.

The major side effects of intravitreal dexamethasone are cataract and raised IOP. Cataract development is more common in diabetic patients and this aspect, although a disadvantage compared to the low risk of cataract development in anti-VEGF use, is unlikely to deter the use of the implant for patients or ophthalmologists in cases with sight threatening DMO. The risk of raised IOP appears to be manageable with topical medication and rarely requires surgical intervention. Similar to cataract this is a relative disadvantage compared to anti-VEGF treatment but is unlikely to deter the use of the therapy in the majority of patients who have no history of advanced glaucoma or uncontrolled ocular hypertension/glaucoma. The risk of the sight threatening complication of infective ophthalmitis is extremely low and comparable to anti-VEGF.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None known

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The intravitreal dexamethasone implant is presently used for macular oedema in the RVO indication in many ophthalmic units throughout England and Wales and thus there is wide experience in its use and monitoring. These units are the same units that would be managing patients with DMO and it is highly likely that it would be widely adopted without significant implementation issues. On the contrary, the use of a longer acting agent compared to existing ranibizumab may have positive benefits on patient care due to reduced burden of injection and monitoring visits.

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Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

None expected