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Single Technology Appraisal (STA)

Aflibercept solution for injection for the treatment of macular oedema caused by central retinal vein occlusion

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: Mr Ian Pearce, Consultant Ophthalmologist

Name of your organisation : Clinical Specialist Nominated by Bayer

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- 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.)?
- other? (please specify)

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

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.

The management of macular oedema secondary to central retinal vein occlusion has changed significantly over the recent years with the introduction of licensed and NICE recommended agents in the form of Dexamethasone intravitreal implants (TA 229) and ranibizumab intravitreal injections (TA 283).

In general, eligible patients are offered a choice of dexamethasone implant or intravitreal ranibizumab. The dexamethasone implant is generally required less often compared to more frequent repeated injections with ranibizumab. Both agents are recommended as options in the RCOphth interim guideline on management of RVO (December 2010). The dexamethasone implant has a higher incidence of intraocular pressure rise and cataract development than the repeated ranibizumab injections but will be required less frequently. These factors influence both patients choice and ophthalmologists recommendations in first line treatment.
Patients who have a tendency for uncontrolled glaucoma or ocular hypertension may be better served by ranibizumab and aflibercept rather than the dexamethasone implant.
There are small case series to suggest that patients not responding to one agent may benefit by switching to the alternative agent.
Observation is much less likely to be used than in the past and may be reserved for cases where the macular oedema is chronic > 2years, where central visual acuity is well preserved such as 6/9 or better or in cases where gross peripheral or foveal ischaemia is present.

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Although Bevacizumab is still used in some centres this would not be considered routine now that licensed and NICE recommended agents are available.

The RCOphth interim guideline on management of RVO (December 2010) does not advocate treatment of macular oedema in the presence of significant retinal ischaemia. The presence of iris neovascularisation was an exclusion criteria in the aflibercept RVO studies and is generally a consequence of gross peripheral retinal ischemia. However, the aflibercept study included atleast 15-30% of patients with areas of significant ischaemia (> 10 disc areas). Thus it is possible that that such levels of ischaemia would still be considered eligible for treatment in UK practice. It is unknown whether aflibercept has a better effect in these patients in comparison to ranibizumab or dexamethasone

The technology is unsuitable for use in primary care settings and should be delivered by an ophthalmologist experienced in medical retinal disorders. It is likely to be delivered in an outpatients' clean room setting similar to its use for AMD, diabetic macular oedema and existing RVO services.

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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?

The introduction of aflibercept for the management of macular oedema in CRVO would be a further significant step forward in the management of patients with RVO in the NHS.
At this stage it is difficult to predict how exactly it will fit alongside dexamethasone and ranibizumab in a patient pathway. It is highly likely that ophthalmologists will wish to offer the choice of all 3 agents to patients. Selective advantage of aflibercept over ranibizumab is difficult as results of head to head trials are not available for RVO. Extrapolating from AMD studies might suggest that the efficacy of aflibercept may be longer than ranibizumab but this is not proven in RVO. If such a longer duration of efficacy was possible then this could be a distinct advantage. The reduced incidence of cataracts and raised intraocular pressure compared to dexamethasone has distinct advantages but as previously stated involves a higher frequency of injections.

Patient pathways will vary from unit to unit but it is likely that patients will have to attend monthly at least for the first 12 months, supplemented with extended intervals after that period for selected patients. Optical Coherence Tomography (OCT) assessment is likely for each of these visits. It is anticipated that the delivery of a service to manage macular oedema in RVO will be similar to service provision for managing exudative AMD with ranibizumab. In essence, this will be repeated out-patients sessions with intermittent PRN injections given in a dedicated outpatient clean room. Many units throughout the UK have ophthalmologists trained in the assessment and management of medical

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retinal disorders such as RVO and will be experienced in managing macular oedema with repeated intravitreal injections.
The introduction of aflibercept should pose no specific difficulties in delivery. However, service provision will be need to meet the minimum requirements outlined in the RCOphth interim guidelines for RVO and include clerical and support services similar to AMD services as proposed in the RCOphth Document "Commissioning Contemporary AMD Services: A guide for commissioners and clinicians July 2007".

The patients enrolled in the pivotal clinical trials reflect the patients likely to present to UK units. In comparison to the ranibizumab trials (CRUISE) the presence of a brisk afferent pupil defect was not considered an exclusion criteria. In addition, the Copernicus aflibercept study included atleast 15-30% of patients with areas of significant ischaemia (> 10 disc areas). It is unknown whether aflibercept has a better effect in these patients in comparison to ranibizumab.

Patients with macular oedema of greater duration than 9 months were excluded from the aflibercept trials and thus the benefit in these patients is unknown. It is likely that they may still benefit from treatment. The pivotal trials of all 3 main agents show improved visual acuity outcomes with earlier treatment and avoiding delay in resolution of the macular oedema.

The safety profile presented is very favourable and consistent with aflibercept use in AMD with minimal significant local or systemic concerns. The long term outcomes for vision and complications are unknown.

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Equality and Diversity

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

No issues identified

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

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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 patient group that may benefit from the aflibercept technology are already attending ophthalmic units for monitoring and treatment with either dexamethasone or ranibizumab. It is likely that patients will have to attend monthly at least for the first 12 months, and subsequently with extended intervals after that period for selected patients. Optical Coherence Tomography (OCT) assessment is likely for each of these visits.

There should be no reason for any delay in implementing delivery of an aflibercept RVO service if a positive FAD is recommended.

Although the introduction of aflibercept as a potential option has occurred since the RCOphth interim RVO guidelines were published it is imperative that the provision and funding of service reflects the standard outlined in those guidelines.

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