

Commissioning Policy: For the Treatment of Wet Age-Related Macular Degeneration and Other Neovascularising Eye Conditions



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1. POLICY STATEMENT

- 1.1. This policy clarifies the role of various agents and interventions in the treatment of wet age - related macular degeneration and other neovascularising eye conditions.

2. EXECUTIVE SUMMARY

- 2.1. Three anti-VEGF (anti-vascular endothelial growth factor) drugs are routinely commissioned by the CCG for the treatment of wet Age-related Macular Degeneration (wet AMD). These are:-
 - **Bevacizumab** (Avastin®)
 - **Ranibizumab** (Lucentis®)
 - Aflibercept (Eylea®)
- 2.2. The CCG believes it is in the interests of patients with wet AMD to make treatment available to more patients than meet the criteria, set out in NICE Technology Appraisal (TA) 155, for treatment with Ranibizumab and TA 294 for treatment with Aflibercept. Ranibizumab and Aflibercept cost significantly more than Bevacizumab (there is an approximate ten-fold cost difference, depending on locally negotiated prices). Given the need to maximise the use of its limited financial resources, the CCG has reached the decision to:
 - treat patients with wet AMD with Ranibizumab and Aflibercept only where they fulfil the criteria set out by NICE in TA 155 and TA 294 **and**
 - treat with **Bevacizumab:**
 - patients with wet AMD who do not fulfil the criteria in TA 155 or TA 294;
 - patients with other ocular conditions which may benefit from anti-VEGF treatment.
- 2.3. If Bevacizumab is not commissioned, large numbers of patients who would benefit from anti-VEGF therapy will not receive any treatment, as they do not meet the criteria set out in NICE TA 155 for treatment with Ranibizumab or NICE TA 294 for treatment with Aflibercept.
- 2.4. Current evidence is consistent with the conclusion that all three agents are equally effective in the treatment of neovascular age-related macular degeneration and there is no convincing evidence of a clinically significant difference in the incidence of serious adverse events between the groups.
 - The CATT Research Group. Ranibizumab and Bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897-908.
 - Ranibizumab versus Bevacizumab to treat neovascular age-related macular degeneration: One-year findings from the IVAN Randomised Trial.

Ophthalmology 2012;119:1399-411.

- Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 2012. 119: 2537-48

2.5 The RCOphth issued a statement in November 2014:

“Two major studies, the CATT2 and the IVAN3 studies, found that an alternative drug, bevacizumab (Avastin), which is licensed for the treatment of some cancers, but does not have a licence for use in AMD, was as effective as the licensed ranibizumab”.¹

2.6 NICE has also mentioned the following in TA294:

In the interests of fairness, it also agreed that the proposed review of the guidance on aflibercept should coincide with the review date for NICE technology appraisal guidance 155, which should also include bevacizumab.

<https://www.rcophth.ac.uk/publications/avastin-bevacizumab/> (2014)

2.7 It is therefore in the interest of the wider vision-impaired patient group that the CCG commissions treatment that allows us to treat all eye conditions which respond to anti-VEGF therapy rather than just a limited number of patients who meet NICE criteria.

- The CCG will routinely fund intravitreal **Bevacizumab** (Avastin) for the following conditions that in the opinion of ophthalmologists require treatment to prevent loss of vision i.e. watchful waiting would not be appropriate:
- Subfoveal, juxtafoveal and extrafoveal choroidal neovascular membrane (CNVM) relating to wet AMD.
- Retinal angiomatous proliferation (RAP).
- Idiopathic polypoidal choroidal vasculopathy (IPCV).
- Myopic CNVM and CNVM due to other pathology.

2.8. The CCG will only routinely fund intravitreal Ranibizumab (Lucentis®) and Aflibercept (Eylea®) strictly in line with NICE TA 155² and 294³ respectively.

2.9. NICE TA 155 states:

- i “Ranibizumab, within its marketing authorization, is recommended **as an option** for the treatment of wet age-related macular degeneration if:
 - All of the following circumstances apply in the eye to be treated:
 - the best-corrected visual acuity is between 6/12 and 6/96
 - there is no permanent structural damage to the central fovea
 - the lesion size is less than or equal to 12 disc areas in greatest linear dimension
 - there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity

changes).

and

- the manufacturer provides Ranibizumab with the discount agreed in the patient access scheme (as revised in 2012).”

2.11. NICE TA 294 states:

2.12 “Aflibercept solution for injection is recommended as an option for treating wet age related macular degeneration only if:

- it is used in accordance with the recommendations for ranibizumab in NICE technology appraisal guidance 155 (re issued in May 2012)

and

- the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme.”

2.13. Where Ranibizumab and Aflibercept are prescribed, clinicians must provide evidence that the patient meets all the NICE criteria through completion of the relevant prior approval proformas. Regular audit will be undertaken to confirm compliance.

2.14. **Photodynamic therapy (PDT)** with Verteporfin may be used for classic with no occult subfoveal CNV that cannot be treated with Ranibizumab due to intolerance or is contraindicated. Patients must fulfil the criteria specified in NICE TA 68.⁴

3. CLINICAL BACKGROUND

3.1. Age related macular degeneration (AMD) is a common cause of visual impairment in the UK and predominantly affects the elderly.

3.2. Estimates from the Royal National Institute of Blind People (RNIB) and the National Institute for Health and Care Excellence (NICE) indicate there may be 26,000 people with exudative or “wet” AMD now eligible for treatment in the UK each year. This would equate to approximately 430 patients across Coventry and Warwickshire.

3.3. There are two forms of AMD:

- Geographic atrophy or dry AMD that causes very gradual loss of vision and
- Neovascular exudative or wet AMD that can cause quite rapid loss of vision.

3.4. The term “wet AMD” encompasses a spectrum of ocular conditions which results in the formation of a choroidal neovascular membrane (CNVM) which forms due to abnormal growth of blood vessels originating in the choroicapillaris, passing through Bruch’s membrane and proliferating in the retina, causing visual loss.

3.5. CNVM can be described in terms of its location in relation to the avascular centre of the fovea. The definition currently in use is based on the Macular Photocoagulation Study (MPS):

- the fovea is the central part of the macula, is avascular and forms the visual fixation point; lesions that develop within the fovea are termed ‘subfoveal’

- ‘extrafoveal’ means that the most central part of the CNVM is $\geq 200\mu\text{m}$ from the avascular centre of fixation
 - ‘juxtafoveal’ means that the CNVM with its furthest central extension is between $200\mu\text{m}$ and $1\mu\text{m}$ from the avascular centre of the fovea, nevertheless leaving the centre unaffected
- 3.6. Neovascularisation can also arise in the retina as opposed to the choroicapillaris and is referred to as retinal angiomatous proliferation (RAP). A highly exudative form of neovascular AMD, mainly diagnosed by ICG Angiography, is known as idiopathic polypoidal choroidal vasculopathy (IPCV).
- 3.7. Wet AMD is treated by anti-VEGF drugs that inhibit the function of a biological growth factor called vascular endothelial growth factor (VEGF) which stimulates angio- and vasculogenesis, causing the wet form of AMD. Such drugs, termed anti-VEGF agents, are given by injection into the eye and most patients need multiple injections at regular intervals to get the desired treatment effect. Anti-VEGF agents can be very effective in treating wet AMD but not all patients respond to treatment. Anti-VEGF agents arrest progression of AMD and may restore some, but not all, of the sight that has been lost.
- 3.8. CNVM may develop in other ocular conditions such as macular telangiectasia, myopic macular degeneration, angioid streaks, presumed ocular histoplasmosis and idiopathic CNVM to name a few.

4. TREATMENT OF WET AMD

Anti-VEGF Drugs

- 4.1. Three anti-VEGF drugs are routinely commissioned by the CCG for the treatment of wet AMD.
- I. **Bevacizumab** (Avastin®) is an anti-VEGF agent that was originally developed for the treatment of cancer, where it is given intravenously. Bevacizumab is licensed for use in cancer treatment and is used internationally as off-label treatment of wet AMD and other eye disorders. It has not been licensed for use within the eye and NICE has been asked to review intra-ocular use after the positive results from the CATT and IVAN studies. It is not marketed by the manufacturers for intra-ocular use and is pharmaceutically aliquoted into the doses required.
 - II. **Ranibizumab** (Lucentis®) is an anti-VEGF agent that has been specifically developed for treatment of wet AMD and clinical trials have proven its efficacy and safety. NICE found it to be cost effective in some patients with wet AMD and approved the use of Ranibizumab within the NHS. Commissioners are legally obliged to fund Lucentis® when an ophthalmologist prescribes it for the treatment of wet AMD **and** if the patient meets all the criteria stated in NICE TA 155.
 - III. Aflibercept (Eyla®) is an anti VEGF agent licensed for use in the treatment of wet AMD. It is recommended for use in accordance with the recommendations for Ranibizumab in NICE TA 155 and where the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme, as stated in NICE TA 294. It has been found to be equally as effective as Ranibizumab.

IV.

- 4.2. Bevacizumab is much cheaper than Ranibizumab, costing the NHS about £30-£50 per injection, with a total cost of £210- £350 in the first year of treatment.
- 4.3. Ranibizumab is expensive and costs the NHS up to £740 per injection (depending on local prices). With an average of 7 injections required per eye in the first year of treatment the total cost of the drug per eye can amount to £5,180. For some patients who need treatment more frequently, the cost of the drug can be considerably more.
- 4.4. Aflibercept is similar in cost to Ranibizumab costing the NHS £816 per injection. An important advantage of aflibercept is that it needs less frequent administration than ranibizumab at a continuation dose of every eight weeks as oppose to every four weeks, thus imposing less burden on patients and carers in terms of time off work and travel costs, as well on the NHS.
- 4.5. RCOphth issued a statement in December 2015:
- “In 2011 a working group of The Royal College of Ophthalmologists released a statement regarding the use of Avastin (bevacizumab) in medical ophthalmology. It found that Avastin and Lucentis (ranibizumab) were equally effective in the treatment of neovascular age-related macular degeneration (AMD) and that there was no convincing evidence of a clinically significant difference in the incidence of serious adverse events between the two.
 - Since 2011, the IVAN trial (2012) has provided further evidence that Avastin is as effective as Lucentis in the treatment of neovascular AMD, and a Cochrane review (2014) comparing the safety of these drugs when used to treat neovascular AMD did not find evidence of a difference for deaths, all serious systemic adverse events (SSAEs), or specific subsets of SSAEs in the first one to two years of treatment with the exception of gastrointestinal disorders.
 - The Cochrane review concluded that, with regard to available data on systemic safety, there was no significant clinical or research evidence to support the preferential use of either Avastin or Lucentis in the treatment of neovascular AMD.
 - There is clear evidence that, despite the lack of a license, Avastin is a safe and effective drug for the treatment of neovascular AMD. The College would therefore welcome an urgent review of this issue by the United Kingdom Health Regulatory Bodies to consider how this unusual situation can be remedied.”⁵
- 4.6. **Having considered this statement**, the CCG has decided to routinely commission Bevacizumab for the treatment of wet AMD, specifically in cases of:
- Neovascular lesions that, in the opinion of ophthalmologists, require treatment to prevent loss of vision i.e. watchful waiting would not be appropriate. This group of patients would include those who meet the criteria in NICE TA 155 or NICE TA 294, but the ophthalmologist considers that treatment with Bevacizumab is in the patient’s best interests (e.g. if the patient has had an adverse response to Ranibizumab).
 - Retinal angiomatous proliferation (RAP) that in the opinion of ophthalmologists requires treatment to prevent loss of vision i.e. watchful waiting would not be appropriate.
 - Idiopathic polypoidal choroidal vasculopathy (IPCV) that in the opinion of

ophthalmologists requires treatment to prevent loss of vision i.e. watchful waiting would not be appropriate.

- Conditions, other than wet AMD, presenting with CNVM that in the opinion of ophthalmologists require treatment to prevent loss of vision i.e. watchful waiting would not be appropriate.

4.7. Intravitreal Bevacizumab must be sourced from a MHRA specialist registered supplier providing manufactured syringes subjected to stability testing. All patients must be informed that an unlicensed product is being used off label and sign a consent form before treatment is initiated.

4.8. A sample patient letter is provided in Appendix 1.

4.9. Ranibizumab and Aflibercept are only routinely commissioned for patients who meet all the criteria in NICE TA 155 and 294:

- Ranibizumab and Aflibercept, within their marketing authorization, are recommended by NICE as an option for the treatment of wet AMD if:
- All of the following circumstances apply in the eye to be treated:
- the best-corrected visual acuity is between 6/12 and 6/96
- there is no permanent structural damage to the central fovea
- the lesion size is less than or equal to 12 disc areas in greatest linear dimension
- there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)

and

- the manufacturers provide ranibizumab and aflibercept with the discount agreed in the patient access scheme.

4.9. To ensure clarity and consistency of application, the following definitions apply for patients receiving Ranibizumab or Aflibercept:

- “Wet AMD” includes patients with subfoveal, extrafoveal, juxtafoveal CNV
- “Permanent structural damage to the central fovea” is indicated by the presence of:
- cilio-retinal anastomoses
- retinal pigment epithelium (RPE) rips involving the fovea and causing loss of vision to less than 25 letters or in the absence of signs of angiographic activity (as there is a risk of large bleeding if untreated)
- sub-retinal fibrosis accounting for more than 50% of lesion
- The presence of one or more of the following is indicative of recent presumed disease progression:
- sub-retinal fluid

- fresh haemorrhage
 - new hard exudates
 - cystoid macular oedema – but needs to be distinguished from intra-retinal cysts
 - increased leakage on fluorescein angiography or increased lesion size
- 4.10. Providers must submit confirmation that patients prescribed Ranibizumab and Aflibercept meet all the NICE criteria in order for the CCG to fund the treatment. This is via the CCGs prior approval system.
- 4.11. If a patient initially receives Bevacizumab but subsequently meets the NICE criteria for Ranibizumab or Aflibercept, they can be switched to Ranibizumab or Aflibercept, if this is clinically indicated.
- 4.12. If a patient requires treatment in both eyes but only meets the criteria for treatment with Ranibizumab or Aflibercept in one eye, clinicians may prefer to use Bevacizumab in both eyes.
- 4.13. A sample patient letter and consent form are provided in **Appendix 1**.

Photodynamic therapy with Verteporfin (PDT)

- 4.14. NICE technology appraisal 68⁴ on PDT restricts use of PDT to patients who have wet AMD with a confirmed diagnosis of “classic with no occult” subfoveal CNV and best corrected visual acuity of 6/60 or better.

5. REFERRAL PATHWAY

- 5.1. Optometrists, General Practitioners, clinicians working in casualty departments and hospital ophthalmology departments should refer any suspected case of wet AMD urgently to a commissioned provider, in line with patient choice.
- 5.2. Patients with wet AMD who are seen at SWFT and GEH and who are considered to require PDT should be referred to UHCW.
- 5.3. **The RCOphth’s guidelines for the management of wet AMD state that treatment must be undertaken without delay and preferably within two weeks of initial development of symptoms or detection of a treatable lesion.**

6. DIAGNOSIS AND MONITORING

Diagnosis

- 6.1. The RCOphth recommends the following diagnostic procedures for retinal imaging in patients suspected of having wet AMD⁶:
- Fundus fluorescein angiography (FFA) is required for making initial diagnosis – it should be used to determine the extent, type, size and location of neovascular lesion.
 - Indocyanine green angiography (ICG) is an additional to FFA. ICG is useful when assessing patients with macular haemorrhage or suspected of having RAP lesions, IPCV, or non-vascularised vs. vascularised pigment epithelial detachments (PEDs).

- Ocular coherence tomography (OCT) with Fourier or Spectral Domain (SD) OCT is mandatory for diagnosis and monitoring response to therapy.

6.2. Standards for the above procedures, as published by the Royal College of Ophthalmologists, should be followed at all times. These should be recorded in the patient's notes or electronic database.

Monitoring

6.3. For Ranibizumab and Bevacizumab

Once treatment has been initiated, at each outpatient visit patients will require:

- Detailed questioning regarding possible serious adverse events from treatment
- Visual acuity measurement (VA)
- OCT
- FFA only if response is not clear from OCT and VA measurements

6.4. For Aflibercept:

- The summary of product characteristics also states that there is no need for monitoring between injections. After the first 12 months of treatment, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating doctor.³

6.5 Although the major studies have treatment and follow up intervals for patients on a monthly basis and others studies as required after three baseline injections or an inject and extend after three baseline injections, it is accepted that treatment and follow up regimes are best individualised for each patient.

Decision to Treat

6.6. It is recommended that ophthalmologists trained in Medical Retinal disease, namely experienced in the management of patients with AMD make all decisions relating to treatment.

Criteria for Continuation of Treatment

6.7 After the three loading doses, Ranibizumab should be continued if:

- a) There is persistent evidence of lesion activity *
- b) The lesion continues to respond to repeated treatment
- c) There are no contra-indications (see below) to continuing treatment

6.8. *Disease activity is denoted by retinal, subretinal, or sub-RPE fluid and/or haemorrhage and/or intra-retinal cysts provided there is no chronic structural change. It is determined clinically by examination, morphologically by OCT and/or lesion growth on FFA, and/or functionally by deterioration of vision.

Drug Holding and Cessation of Therapy

- Consider temporarily discontinuing treatment if:
 1. There is no disease activity

The disease should be considered to have become inactive when there is:

- a) Absence of FFA leakage and no increase in lesion size, new haemorrhage or exudates, although persistent fluid on OCT can be due to chronic structural change and /or
- b) OCT indicators of CNV disease activity on subsequent follow up following recent discontinuation of treatment and /or
- c) No additional lesion growth or other signs of new disease activity on subsequent follow up following recent discontinuation of treatment and /or
- d) Stable vision or deterioration in vision not attributed to CNV activity.

OR

2. There has been one or more serious adverse events (SAEs) related to drug or injection procedure including:

- a) Endophthalmitis
 - b) Retinal detachment
 - c) Severe uveitis
 - d) Ongoing peri-ocular infections
 - e) Other serious ocular complications attributable to anti-VEGF treatment
 - f) Thrombo-embolic phenomena, including MI or CVA in the preceding 3 months, or recurrent thrombo-embolic phenomena where anti-VEGF treatment is considered to put the patient's life at risk.
 - g) Other SAE e.g. hospitalisation
- Consider discontinuing treatment permanently if:
 1. A **hypersensitivity** reaction to anti-VEGF drugs is established or suspected or
 2. Severe best corrected visual acuity (BCVA) loss in the treated eye of **>15 letters on 2 consecutive visits** due to AMD or
 3. **BCVA loss of ≥ 30 letters** compared to baseline and/or BCVA since baseline as this may indicate either poor treatment response and/or adverse event or
 4. Deterioration of the **lesion morphology** despite optimum treatment. Evidence includes progressive increase in lesion size confirmed with FFA, worsening of OCT indicators of CNVM activity or other evidence of disease activity in the form of significant new haemorrhage or exudates despite optimum therapy over 3 consecutive visits.

7. SERVICE DELIVERY

7.1. It is expected that anti-VEGF treatment will be administered on an outpatient appointment basis. On initiation of treatment and after each hospital visit, a correspondence letter should be sent to the patient's General Practitioner (GP). Information on further

management in the event of a problem should also be provided.

8. AUDIT

8.1. Quarterly audit of cases is required to provide the following information:

- Total number of cases treated with Bevacizumab
- Total number of cases treated with Ranibizumab
- Total number of cases treated with Aflibercept
- Clinical/ surgical and systemic complication rates for each anti-VEGF drug
- Number of cases where treatment has been discontinued and reason why.

9. REFERENCES

1. RCOphth. The Royal College of Ophthalmologists recommends UK regulatory bodies appraise the use of bevacizumab for age related macular degeneration potentially saving the NHS over £100million a year. Press release: 19 November 2014.
2. NICE. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. NICE technology appraisal guidance 155, August 2008 (last modified May 2012).
3. NICE. Aflibercept solution for injection for treating wet age-related macular degeneration. NICE technological appraisal guidance (TA 294). 24 July 2013
4. NICE. Guidance on the use of photodynamic therapy for age related macular degeneration. NICE technology appraisal guidance 68, September 2003.
5. RCOphth. Statement – The use of Avastin (bevacizumab) in age related macular degeneration December 2015
6. RCOphth. Age related macular degeneration – guidelines for management. February 2013.

10. APPENDIX 1: PATIENT INFORMATION – TO BE GIVEN ALONGSIDE THE TRUST’S PATIENT INFORMATION LEAFLET ON WET AMD

Patient Information on the Use of Bevacizumab (Avastin) in Wet AMD

1. HOW IS WET AMD TREATED?

If you have wet AMD you may be suitable for treatment with a drug containing anti-vascular endothelial growth factor (anti-VEGF).

Three anti-VEGF drugs are available to ophthalmologists:

- Bevacizumab (Avastin®)
- Ranibizumab (Lucentis®)
- Aflibercept (Eylea®)

2. USING AVASTIN FOR TREATING AMD

Ranibizumab (Lucentis®) is an anti-VEGF agent that has been specifically developed for treatment of eye conditions and has been shown in clinical trials to be effective in the treatment of „wet“ AMD. It also has a very good safety record. It has been evaluated by the National Institute for Clinical Excellence (NICE) and found to be cost effective (if used in line with the tight criteria specified by

NICE). NICE has approved Lucentis for use within the NHS and Clinical Commissioning Groups (CCGs) are legally obliged to fund Lucentis when an ophthalmologist prescribes it for the treatment of AMD if the patient meets the NICE criteria.

Lucentis® is expensive and costs the NHS £740 per injection (list price although a confidential patient access scheme has been agreed). With an average of 7 injections required per eye in the first year of treatment the total cost of the drug per eye can amount to £5,180. For some patients who need treatment over a longer period, the cost of the drug can be considerably more.

Bevacizumab (Avastin®) is an anti-VEGF agent that was originally developed for the treatment of cancer, where it is given intravenously. It has a similar mode of action to Lucentis®. Avastin® is licensed for use in cancer treatment and has been used widely around the world for treatment of wet AMD and other eye disorders. It has not been licensed or approved by NICE for use within the eye. It is not marketed by the manufacturers for treatment of eye disorders or prepackaged in the very much smaller doses required for injection into the eye (specialist pharmacies have been splitting phials of the drug supplied by the manufacturer).

Avastin is much cheaper than Lucentis, costing the NHS about £60 per injection, with a total equivalent cost of £420 in the first year of treatment. This makes it more affordable and means it can be offered to a larger group of patients with wet AMD than NICE has approved Lucentis for.

3. CHOOSING WHICH AGENT TO USE

If you do not meet the NICE criteria for Lucentis® or Eylea® but your consultant believes you need treatment with an anti-VEGF drug, they may offer you Avastin®.

International clinical trials, namely the CATT and IVAN studies, compared Avastin® and Lucentis® and found Avastin® is as effective as Lucentis® in wet AMD.

Avastin® will be offered routinely to patients who require treatment and **do not** meet the NICE criteria for Lucentis® and Eylea® (which will only be offered to patients with wet AMD who meet all the criteria specified by NICE). The Avastin® will be sourced from a reputable pharmacy and you will be asked to give consent that you agree to the treatment.

If you have questions, please ask the ophthalmology consultant on your clinic visit.