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Norfolk and Waveney Integrated Care System

LATE WET AGE-RELATED MACULAR DEGENERATION PATHWAY 2022

Norfolk and Waveney Integrated Care System

1. Table of Contents

2. Document Control Sheet

Name of document:	Late wet age-related macular degeneration pathway 2023
Description of policy	N&WICB high-cost drug pathway for late wet AMD
Version	1.0
Scope	
Prepared by	Medicine optimisation team with input/advice from specialists at NNUH, QEH & JPH
Impact Assessment (Equalities and Environmental)	
Other relevant approved documents	
Evidence base / Legislation	Level of Evidence: ~~A. based on national research-based evidence and is considered best evidence~~ **B. mix of national and local consensus** ~~C. based on local good practice and consensus in the absence of national research based information.~~
Dissemination	Is there any reason why any part of this document should not be available on the public web site? ~~Yes~~ / **No**
Approved by	N&WICB Therapeutics advisory group
Authorised by	N&WICB Therapeutics advisory group
Review date and by whom	June 2025
Date of issue	07/06/2023

2.1 Revision History

Revision Date	Summary of changes	Author(s)	Version Number
15/06/2022	First draft of pathway	A. Charlwood, M. Sully	0.1
14/10/2022	Comments from local specialists included into pathway	As above & local specialists	0.2
03/03/2023	Inclusion of biosimilar, and Faricimab. Amendments to treatment algorithm, inclusion of summary document	As above	0.3
07/06/2023	Approved by TAG	As above	1.0

2.2 Approvals

This document requires the following approvals either individual(s), group(s) or board.

Name	Title	Date of Issue	Version Number
Norfolk & Waveney ICB Therapeutics Advisory Group		07/06/2023	1.0

3. Introduction

3.1 Relevant NICE technology Appraisals

Technology Appraisal*	Title
TA155	Ranibizumab and pegaptanib for the treatment of age-related macular degeneration
TA294	Aflibercept solution for injection for treating wet age-related macular degeneration
TA672	Brolucizumab for treating wet age-related macular degeneration
TA800	Faricimab for treating wet age-related macular degeneration

*NICE recommendations **also apply to biosimilar products of the technologies** that have a marketing authorisation, allowing the use of the biosimilar for the same indication.

3.2 Pathway scope

This pathway, using up to date published NICE Technology Appraisals (TAs) and evidenced based medicine, is a guide to the initiation and maintenance of high-cost drugs in the management of diabetic macular oedema (DMO).

The pathways include biologic agents:

- Anti-VEGFs (Aflibercept, Ranibizumab & Brolucizumab)
- Anti-VEGF & Ang-2 (Faricimab)

Drugs should be used in accordance with the relevant TA. The links are included in this document. Inclusion will be allowed for any new high-cost drugs that are approved by NICE prior to review of the pathway, provided that the relevant local "New Medicines" Policy and process has been followed. Those drugs should be used in accordance with the relevant NICE TA. The NICE recommendations also apply to biosimilar drugs, where marketing authorisations allow use of the biosimilar for the indication specified in the relevant NICE TA.

3.3 Classification

nAMD is classified by the following characterisations:

- Classic choroidal neovascularisation (CNV)
- Occult (fibrovascular pigment epithelial detachment (PED) and serous PED with neovascularisation)
- Mixed (predominantly or minimally classic CNV with occult CNV)
- Retinal angiomatous proliferation (RAP)
- Polypoidal choroidal vasculopathy (PCV)

4. When to use anti-VEGF treatment

All intravitreal anti-VEGF treatment[1] for late AMD (wet active) are recommended for use based on the following criteria specified in NICE TA155 for Ranibizumab:

4.1 Inclusion criteria

- ✓ The best-corrected visual acuity is between 6/12[a] and 6/96[b]
- ✓ 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
    - For example, blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)

4.2 Exclusion criteria

- × Hypersensitivity to the active substances or excipients
- × Active/suspected ocular/periocular infections
- × Significant ocular inflammation

4.2.1 Adjunctive therapies

Only offer photodynamic therapy as an adjunct to anti-VEGF as second-line treatment for late AMD (wet active) in the context of a randomised controlled trial.

4.2.1.1 Do not offer

- × Photodynamic therapy alone for late AMD (wet active).
- × Photodynamic therapy as an adjunct to anti-VEGF as first-line treatment for late AMD (wet active).
- × Intravitreal corticosteroids as an adjunct to anti-VEGF for late AMD (wet active).

5. Monitoring

5.1 General recommendations (Royal College of Ophthalmologists, 2021)

Self-monitor their AMD -but please note that utilising visual function changes to monitor new or recurrent disease is not sufficiently sensitive.

- Consult their eye-care professional as soon as possible if their vision changes
- Continue to attend routine sight-tests with their primary care optometrist.
- OCT is the most sensitive monitoring tool. For community provision, OCT should be used to monitor patients that are at high risk of new wet AMD or being monitored for stable wet AMD.
- Be provided information about sources of support for living with sight loss including local and national charities.
- Be made aware of the local Eye Clinic Liaison Officers (ECLO) service, and how to re-access emotional and practical support. This would include advice on Certification and Registration.

5.2 Self-Monitoring

Patients with AMD should be counselled by a trained HCP regarding the strategies available. Patients should be reminded that none of the strategies for home monitoring of visual function are currently sufficiently sensitive to detect disease recurrences and that optical coherence tomography (OCT), is the most sensitive detection tool (Royal College of Ophthalmologists, 2021). Patients with AMD should report any new symptoms or changes regarding their central vision to their eye-care professional as soon as possible:

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[a] Be aware that anti-VEGF treatment for eyes with late AMD (wet active) and visual acuity better than 6/12 is clinically effective and may be cost effective depending on the regimen used.

[b] In eyes with visual acuity of 6/96 or worse, consider anti-VEGF treatment for late AMD (wet active) only if a benefit in the person's overall visual function is expected (for example, if the affected eye is the person's better-seeing eye).

- blurred or grey patch in their vision
- straight lines appearing distorted
- objects appearing smaller than normal

5.3 Baseline Monitoring

Through following assessments be completed:

- BCVA (preferably in ETDRS letters)
- OCT
- OCT-angiography (OCT-A) and/or fundus fluorescein angiography (FFA)/ Indocyanine green angiography (ICG)
- Intraocular pressure (IOP)
    - If patient has persistent ocular hypertension, they should be referred to the glaucoma team for management.

5.4 Routine Monitoring

- Both eyes should be assessed at monitoring appointments. OCT should be the primary diagnostic indicator.
    - BCVA (preferably in ETDRS letters)
    - OCT
- Routine IOP testing post injection is not recommended but annual IOP monitoring is required to identify sustained IOP rise from repeated injections. If OCT appearances are stable, but there is one of the following:
    - A decline in visual acuity
    - Patient reports a decline in visual function
- Offer **fundus examination(?)** or **colour photography(?).** Consider FFA to identify unrecognised neovascularisation. If OCT results suggest macular abnormalities but the abnormalities are not responding to treatment, consider alternate diagnosis.

6. Choice of Anti-VEGF

As per NHS England:

"Subject to the criteria specified in the relevant NICE technology appraisal guidance, clinicians should consider **ranibizumab biosimilar where this is clinically appropriate and there is capacity to do so**.

If ranibizumab biosimilar is contraindicated or not clinically appropriate for the specific patient or there are specific clinical considerations (such as non-responder to ranibizumab in fellow eye previously, subretinal bleed >50% of lesion, idiopathic polypoidal choroidal vasculopathy (PCV)) then, subject to the criteria specified in the relevant NICE technology appraisal guidance, clinicians should consider aflibercept, brolucizumab or faricimab"[1]

6.1 Dosing interval

6.2 Ranibizumab biosimilar (Byooviz)

- BYOOVIZ 0.5 mg (0.05 mL of 10 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).
    - Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing with regular assessment.
    - In the 9 months after three initial monthly doses, less frequent dosing with 4-5 doses on average is expected to maintain visual acuity while monthly dosing may be expected to result in an additional average 1-2 letter gain. Patients should be assessed regularly.
    - Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Compared with continued monthly dosing, dosing every 3 months over the next 9 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average. Patients should be assessed regularly

6.3 Ranibizumab local recommendation (TAG)

- Offer monthly injections for three months, reassess, and if needed continue with monthly intervals until there are no signs of disease activity on OCT.
    - The effects of ranibizumab should peak at 3 months (NICE, 2012).
- Once that is achieved continue with treatment, increasing the treatment intervals by 2/52 between each injection until a maximum interval of 12/52
    - If signs of recurrence on OCT or VA loss (5 letters or more), reduce treatment interval by 2/52 and monitor
    - Patients requiring more than 8 injections of Ranibizumab in the last 12 months can change to Aflibercept if considered appropriate as per TAG recommendation

6.4 Aflibercept

- Treatment to be commenced with 1 injection every month for 3 months followed by injections every 2 months.
    - Monitoring and treatment frequency are to be determined by the treating physician based on disease activity (assessed using VA, clinical examination, OCT and/or OCT-A and/or FFA).
- For treat-and-extend regimens, treatment interval may be increased by 2-4 weeks every successive visit (up to maximum inter-treatment interval of 16 weeks) unless signs of activity or decrease in VA are noted where interval may be reduced to no less than 4-weekly.
    - Trial without treatment may be considered when no disease activity or VA reduction are noted on three consecutive visits at 16-week treatment interval

6.5 Faricimab

- Treatment to be commenced with 1 injection every 4-weeks for 4 doses.
    - Thereafter, an assessment of disease activity based on anatomic and/or visual outcomes is recommended 20 and/or 24 weeks after treatment initiation so treatment can be individualised.
- In patients without disease activity, treatment should be extended to 16-weekly intervals
- In patients with disease activity, treatment at 8-weekly or 12-weekly intervals should be considered.

6.6 Brolucizumab

- Treatment to be commenced with 1 injection every 4-weeks for 3 doses.
    - A disease activity assessment is suggested 16 weeks (4 months) after treatment start.
- In patients without disease activity, treatment every 12 weeks (3 months) should be considered.
- In patients with disease activity, treatment every 8 weeks (2 months) should be considered
- Not included in algorithm due to local clinical preference

7. Non responders (Royal College of Ophthalmologists, 2021)

A non-responder is defined as a patient whose visual acuity declines due to persistent activity of the neovascular complex despite optimally delivered treatment regimen.

1. The diagnosis should be re-evaluated as very few patients with active wet AMD do not respond to anti-VEGF therapy.
    a. This may require additional imaging with FFA and/or ICG angiography where applicable.
2. The most likely reason for non-response is inadequate therapy due to protocol deviations. Therefore, to avoid further loss, adhere strictly to a re-loading followed by treat and extend protocol.
    a. Failsafe admin processes should be available to track patients with poor compliance due to co-morbidities.
3. A switch to another anti-VEGF agent is recommended in cases of allergy or presumed tachyphylaxis.
    a. In a small minority, a patient may require a switch back to previous agent or to another agent if disease worsens after the initial switch.
    b. There are practical reasons for switching regimens. For example, it may be easier to switch to a fixed regimen rather than a treat and extend protocol in some individuals to aid adherence to treatment.

4. As new treatments emerge it would be worth evaluating the effectiveness based on efficacy (improved visual or anatomical outcomes) or decrease in treatment burden.
    a. Agents with a reduced treatment burden are particularly helpful for patients with co-morbidities affecting compliance and are also useful to allow timely service delivery of care.

8. Switching Anti-VEGF therapy

8.1 High frequency switching thresholds (Faricimab & Brolucizumab to be commissioned)

Biologic	Treatments per year
Ranibizumab	8
Aflibercept	8
Faricimab	6
Brolucizumab	6

8.2 Local TAG pathway

1. Patients requiring more injections annually than noted in section 8.1, can change to another treatment if considered appropriate.
2. **Intolerance to ranibizumab or aflibercept** - It is appropriate to change to the other treatment using the following definition of intolerance:
    a. Persistent sub-retinal or intra-retinal fluid on several consecutive occasions despite repeated intravitreal injections **OR**
    b. Where continued use of ranibizumab or aflibercept is unsuitable because of an allergic response, and, where there is still potential for improvement in vision with further treatment.
3. Inadequate response
    a. It is appropriate to switch treatment if there has been insufficient clinical benefit after optimum treatment, and the treating clinician believes switching may yield a better response.

8.3 Switching long term users of Anti-VEGF

- Deteriorating response in long term users…
    - … who develop drug tolerance over time.
    - …. with prior sub-optimal response to Aflibercept and Ranibizumab.

9. Treatment discontinuation (Royal College of Ophthalmologists, 2021)

The NICE guidelines indicate that it was appropriate to stop anti-VEGF treatment…

9.1 If an eye met the defined criteria of late AMD wet inactive:

✓ Fibrous scar
✓ Sub foveal atrophy or fibrosis secondary to an RPE tear
✓ Atrophy (absence or thinning of RPE and/or retina)
✓ Cystic degeneration (persistent intraretinal fluid or tubulations unresponsive to treatment)

N.B. Eyes may still develop or have a recurrence of late AMD (wet active)

Fellow eyes of those eyes that have discontinued treatment due to wet inactive disease would be discharged from HES **and/or:**

✓ If it was determined that there was no prospect of visual improvement from continued treatment.

9.2 Cause for permanent discontinuation due to treatment failure include:

✓ A hypersensitivity reaction is established or suspected

- ✓ Reduction of BCVA in the treated eye to less than 15 letters (absolute) on two consecutive visits in the treated eye, attributable to AMD in the absence of other pathology
- ✓ Reduction in BCVA of 30 letters or more compared with either baseline and/or best recorded level since baseline
    - this may indicate either poor treatment effect or adverse event or both
- ✓ There is evidence of deterioration of the lesion morphology despite optimum treatment.
    - Such evidence includes progressive increase in lesion size confirmed with FFA, worsening of OCT indicators of CNV disease activity or other evidence of disease activity in the form of significant new haemorrhage or exudates despite optimum therapy over three consecutive visits.

Premature treatment discontinuation and inefficient treatment are important causes of visual loss and should be avoided.

- On an average, a patient initiated on treatment would require
    - 8 injections in the first year
    - 6 injections in the second year
    - 5 injections from the third year onwards are required to prevent decrease in vision due to inadequate treatment.

Individualised care is recommended with some requiring more and others requiring fewer injections.

10. Interchangeability

As per MHRA guidelines:

"Once authorised, **a biosimilar product is considered to be interchangeable with their [reference product (RP)]**, which means a prescriber can choose the biosimilar medicine over the RP (or vice versa) and expect to achieve the same therapeutic effect**. Likewise, a biosimilar product is considered to be interchangeable with another biosimilar to the same RP**.

As a result of interchangeability, switching patients from one product to another (RP or biosimilar) has become clinical practice. The decision rests with the prescriber in consultation with the patient, in line with the principles of shared decision making; both need to be aware of the brand name of the product received."[2]

11. Pregnancy

There is limited data for safety of biologic medicines in pregnancy and breastfeeding. The decision to continue biologic medicines throughout pregnancy must be individualised. This should consider the various therapies, severity of the mother's health prior to therapy, risk of a disease flare if therapy is discontinued, and the impact of a disease flare on the mother and unborn child. This should be discussed by a multi-disciplinary team. Patients who discontinue treatment during pregnancy should resume biological therapy as soon as possible following delivery.

11.1 Choice of therapy for patients planning to conceive

See the table below for further details on specific biologics in the different stages of pregnancy, information collated from the BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding[3], and SPC of the relevant biologic.

	Compatible with trimester		
Drug	1st	2nd	3rd
Ranibizumab	No, use effective contraceptive during treatment.		
Aflibercept	No, use effective contraceptive during treatment.		
Faricimab	No, use effective contraceptive during treatment.		
Brolucizumab	No, use effective contraceptive during treatment.		

11.2 Breastfeeding

There is little information available regarding the excretion of biologics in breast milk. Immunoglobulins are excreted in human breast milk, so a risk to a child cannot always be ruled out. The decision to breastfeed or continue/discontinue therapy should consider both the benefits of breastfeeding to the infant and the benefits of therapy to the mother.

See the table below for further details on specific biologics in breastfeeding, information is taken from the SPC of the relevant biologic. Where no data or recommendation is provided, it would be appropriate to use the "Time to stop treatment prior to surgery" listed in section 11 to determine time between discontinuing treatment and starting breastfeeding.

Biologic	Compatible with Breastfeeding
Ranibizumab	No data – not recommended
Aflibercept	No data – not recommended
Faricimab	No data – not recommended
Brolucizumab	No data – not recommended

12. Correspondence

12.1 Information to be included in correspondence from secondary to primary care:

- Main diagnosis/diagnoses
- Date(s) of intervention
- Secondary diagnosis/diagnoses
- Date of last examination, with findings & timing of next planned review/ contact with secondary care
- Current medical therapy including any previous treatments within pathway (including non-biologics)
- Recommended length of current medical therapy

12.2 Information to be included in correspondence from primary to secondary care:

- Date last prescription issued
- All current and recent medications.
- Functional impact e.g., impact on employment, family, and social functioning
- Any newly diagnosed co-morbidities

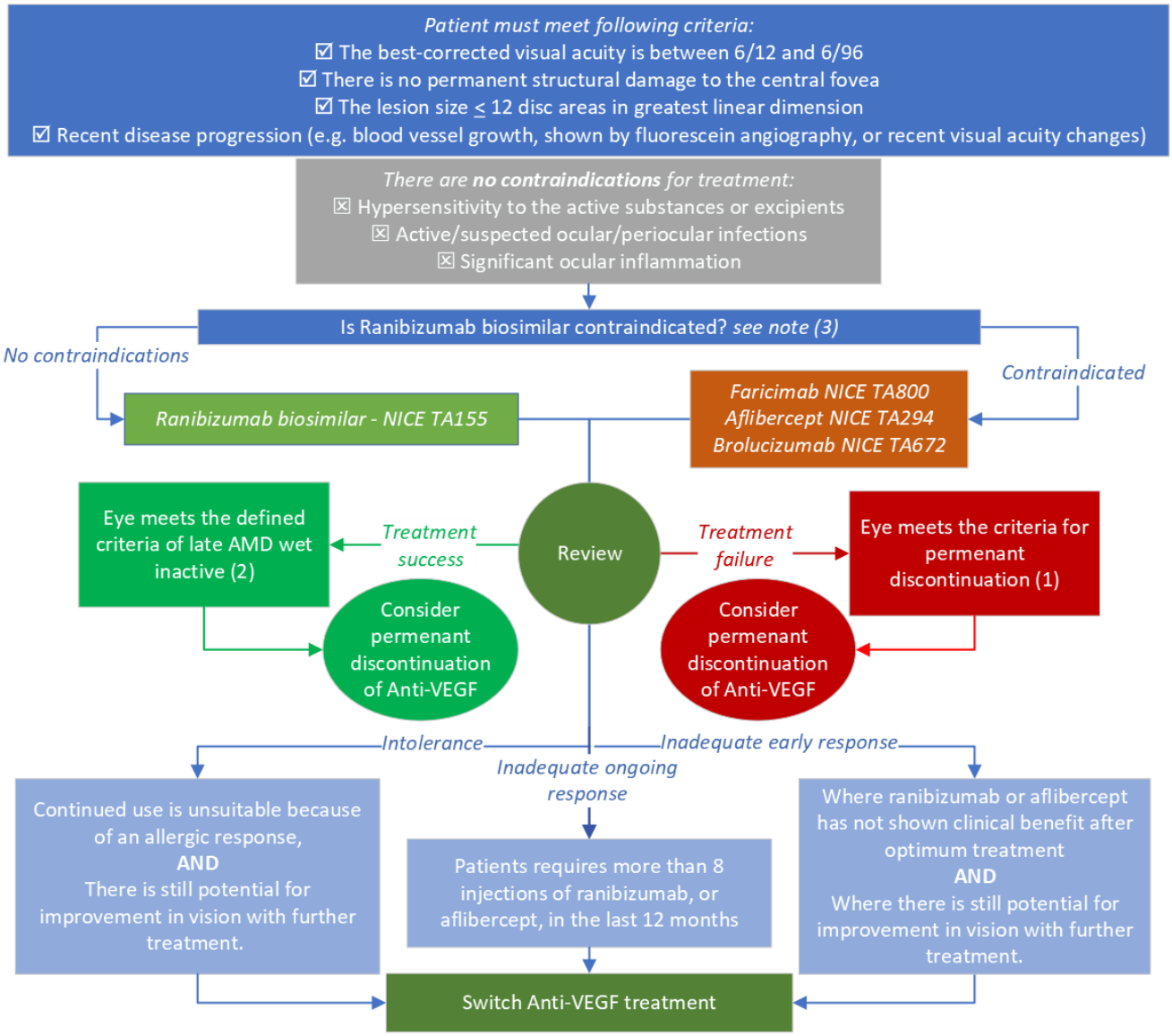
13. References

1. NHS England. Commissioning recommendations national procurement m following edical r etinal medicines. Published online August 2022. https://www.england.nhs.uk/wp-content/uploads/2022/08/B1720-Commissioning-recommendations-following-national-procurement-medical-retinal-vascular-medicines-August-2.pdf

2. Medicines & Healthcare products Regulatory Agency. Guidance on the licensing of biosimilar products. GOV.UK. Accessed July 1, 2022. https://www.gov.uk/government/publications/guidance-on-the-licensing-of-biosimilar-products/guidance-on-the-licensing-of-biosimilar-products

3. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology*. 2016;55(9):1693-1697. doi:10.1093/rheumatology/kev404

14. Appendix 1 – nAMD flowchart



(1). Further details on cause for permanent discontinuation due to treatment failure include:

- A hypersensitivity reaction is established or suspected
- Reduction of BCVA in the treated eye to less than 15 letters (absolute) on two consecutive visits in the treated eye attributable to AMD in the absence of other pathology
- Reduction in BCVA of 30 letters or more compared with either baseline and/or best recorded level since baseline
- There is evidence of deterioration of the lesion morphology despite optimum treatment. Such evidence includes progressive increase in lesion size confirmed with FFA, worsening of OCT indicators of CNV disease activity or other evidence of disease activity in the form of significant new haemorrhage or exudates despite optimum therapy over three consecutive visits.

(2) Defined criteria of late AMD wet inactive:

- Fibrous scar
- Sub foveal atrophy or fibrosis secondary to an RPE tear
- Atrophy (absence or thinning of RPE and/or retina)
- Cystic degeneration (persistent intraretinal fluid or tubulations unresponsive to treatment)

(3) If ranibizumab biosimilar is contraindicated or not clinically appropriate for the specific patient or there are specific clinical considerations (such as non-responder to ranibizumab in fellow eye previously, subretinal bleed >50% of lesion, idiopathic polypoidal choroidal vasculopathy (PCV)) then, subject to the criteria specified in the relevant NICE technology appraisal guidance, clinicians should consider aflibercept, brolucizumab or faricimab.

15. Appendix 2 – NICE technology appraisal detail

TA155	Ranibizumab and pegaptanib for the treatment of age-related macular degeneration 1. Ranibizumab, within its marketing authorisation, is recommended as an option for the treatment of wet age-related macular degeneration if: 1.1. all of the following circumstances apply in the eye to be treated: 1.2. the best-corrected visual acuity is between 6/12 and 6/96 1.3. there is no permanent structural damage to the central fovea 1.4. the lesion size is less than or equal to 12 disc areas in greatest linear dimension 1.5. there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes) 1.6. and 1.7. the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012). 2. It is recommended that treatment with ranibizumab should be continued only in people who maintain adequate response to therapy. Criteria for discontinuation should include persistent deterioration in visual acuity and identification of anatomical changes in the retina that indicate inadequate response to therapy. It is recommended that a national protocol specifying criteria for discontinuation is developed. 3. Pegaptanib is not recommended for the treatment of wet age-related macular degeneration. 4. People who are currently receiving pegaptanib for any lesion type should have the option to continue therapy until they and their clinicians consider it appropriate to stop.
TA294	Aflibercept solution for injection for treating wet age-related macular degeneration 1. Aflibercept solution for injection is recommended as an option for treating wet age-related macular degeneration only if: 1.1. it is used in accordance with the recommendations for ranibizumab in NICE technology appraisal guidance 155 (re-issued in May 2012) and 1.2. the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme. 2. People currently receiving aflibercept solution for injection whose disease does not meet the criteria in 1 should be able to continue treatment until they and their clinician consider it appropriate to stop.
TA672	Brolucizumab for treating wet age-related macular degeneration 1. Brolucizumab is recommended as an option for treating wet age-related macular degeneration in adults, only if, in the eye to be treated: 1.1. the best-corrected visual acuity is between 6/12 and 6/96 1.2. there is no permanent structural damage to the central fovea 1.3. the lesion size is less than or equal to 12 disc areas in greatest linear dimension and 1.4. there is recent presumed disease progression (for example, blood vessel growth, as shown by fluorescein angiography, or recent visual acuity changes). 1.5. It is recommended only if the company provides brolucizumab according to the commercial arrangement. 2. If patients and their clinicians consider brolucizumab to be one of a range of suitable treatments, including aflibercept and ranibizumab, choose the least expensive (taking into account administration costs and commercial arrangements). 3. Only continue brolucizumab in people who maintain an adequate response to therapy. Criteria for stopping should include persistent deterioration in visual acuity and identification of anatomical changes in the retina that indicate inadequate response to therapy.

	4. These recommendations are not intended to affect treatment with brolucizumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them.
TA800	Faricimab for treating wet age-related macular degeneration 1. Faricimab is recommended as an option for treating wet age-related macular degeneration in adults, only if: 1.1. the eye has a best-corrected visual acuity between 6/12 and 6/96 1.2. there is no permanent structural damage to the central fovea 1.3. the lesion size is 12 disc areas or less in greatest linear dimension 1.4. there are signs of recent disease progression (for example, blood vessel growth as shown by fluorescein angiography, or recent visual acuity changes) 1.5. the company provides faricimab according to the commercial arrangement. 2. If patients and their clinicians consider faricimab to be 1 of a range of suitable treatments (including aflibercept and ranibizumab), choose the least expensive treatment. Take account of administration costs, dosage, price per dose and commercial arrangements. 3. Only continue faricimab if an adequate response to treatment is maintained. Criteria for stopping should include persistent deterioration in visual acuity and anatomical changes in the retina. 4. These recommendations are not intended to affect treatment with faricimab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.